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Development, Characterization, and Technology Transfer of Liquid-Infused Catheters

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DEVELOPMENT, CHARACTERIZATION, AND TECHNOLOGY TRANSFER OF LIQUID-INFUSED CATHETERS

By

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A THESIS

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Thesis Advisor: Dr. Caitlin Howell

An Abstract of the Thesis Presented
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Hospital-acquired infections (HAIs) affect over 1.7 million patients annually and are often treated with antibiotics, which can contribute to antibiotic resistance. Catheter-associated urinary tract infections (CAUTIs) are the most common type of HAI, resulting in an estimated $390–$450 million in treatment and increased length-of-stay-associated costs annually. Previously, infusing catheter surfaces with a compatible liquid has demonstrated the ability to reduce the need for antibiotics by minimizing protein and bacterial adhesion to the catheter surface. In this work, we infuse commercial catheters with liquid to investigate changes in properties such as length, mass, and overall size. Confocal microscopy was used to examine the material and coating interface, while tensile and Shore hardness testing was conducted to quantify bulk material properties after coating application. The functionality of these devices was then tested following ASTM F623-19: Performance for Foley Catheter guidelines. By developing liquid-infused treatments for commercial catheters, we aim to create a widely available, cost-effective solution for preventing CAUTI and reducing antibiotic use in patients who need indwelling catheters.

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INTRODUCTION

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1.1.1 The Urinary System and Urinary Catheters

The urinary system functions to filter waste products and excess liquids from the blood and expel them from the body in the form of urine.[1,2] The urinary system (Figure 1.1) comprises the kidneys, ureters, bladder, and urethra. An estimated 37.5 gallons of blood pass through and are filtered by the kidneys daily, removing waste products from the blood. Urea—waste filtered out of the blood by the kidneys—is sent from the kidneys to the bladder by synchronized contractions of the ureters and is stored until release.[2] Stretch cells, or cells that respond to the stretching of surrounding tissue, detect fluctuations in bladder volume due to the accumulation of urine and transmit signals to the brain to relax the internal and external sphincter muscles of the bladder while the bladder muscles contract simultaneously.[1,3] This results in urine exiting the body through the urethra.

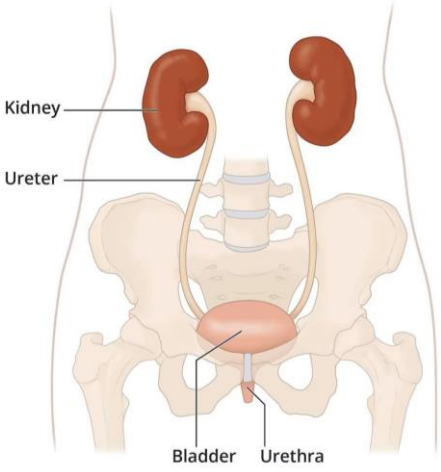

Figure 1.1. Components of the urinary system. Photo credit: National Institute of Diabetes and Digestive and Kidney Diseases.

There are a variety of conditions that can interrupt the normal function of the urinary system. Urinary catheters are medical devices that facilitate urine drainage from the body in patients who cannot do so normally,[4,5] as failure to urinate can result in pressure build-up within the bladder, which can cause kidney failure over time.[5] Urinary catheters are used to treat abnormal urinary function in patients with conditions such as neurological disorders like multiple sclerosis or spinal cord injuries where the transmission of signals between the muscles involved with urination and the brain can become impaired, resulting in urinary retention.[4] Similarly, individuals who have obstructed flow due to an enlarged prostate or who are comatose

can suffer from urinary retention.[4] Individuals with degenerative conditions such as dementia and Alzheimer's disease can have difficulty controlling their bladder function as desired, known as urinary incontinence.[3] Additionally, the strength of the bladder and sphincter muscles decreases with age, and many older adults in nursing homes are catheterized to treat incontinence.[1,6] Commonly, individuals who are undergoing urogenital surgery, surgical procedures requiring anesthesia, or of extended duration are catheterized.[6]

1.1.2 Types of Urinary Catheters

Anywhere from 12–25% of hospitalized patients will be catheterized at some point during their stay.[5,7–9] To meet the many different patient procedural needs, many variations of catheters have been developed, each with specific intended uses. Each type of catheter is sized by its outer diameter—expressed as French (Fr)—allowing for choice of both model and size to further cater to patient needs. The equivalent of one Fr is 0.33 millimeters (mm). Clean intermittent self-catheterization (Figure 1.2A)[10] is ideal for patients with chronic urinary retention who possess the ability to self-catheterize. These devices are meant to mimic the normal function of the urinary system, where a patient will insert the catheter themselves, prompting the drainage of urine from the bladder into a collection bag or toilet bowl throughout insertion.[3] This process is typically done four to six times per day, depending on the patient's needs, the physician's instruction, or the amount of product covered by the respective insurance companies.[11] These catheters can be either single-use or reusable.

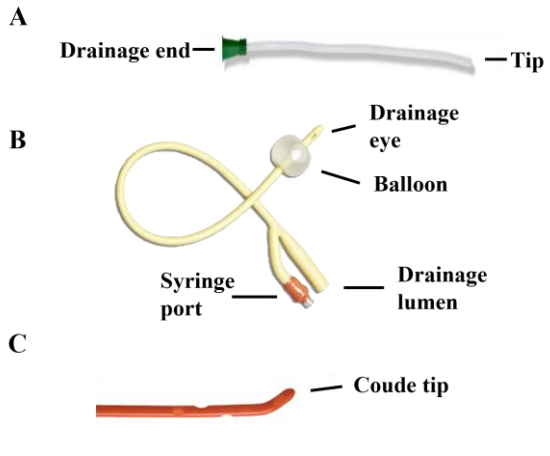

Figure 1.2. Types of urinary catheters.

Images of (A) Intermittent catheter; (B) Indwelling Foley Catheter; and (C) Coude tipped catheters available to meet individual patient needs. Image credit: (A) Bard BD Straight Tip Intermittent Catheter – Male; (B) Dover, Foley Catheter; Coloplast Coude Tip Catheter. Adapted from Fong (2024).[10]

Indwelling catheters are used in patients who cannot self-catheterize and are intended to continually drain urine from the bladder for greater than 24 hours.[6] Most commonly, this is the Foley catheter (Figure 1.2B), designed with two inner lumens, each with a specific purpose. The first lumen is the conduit for the drainage of urine, connecting the drainage eye at the tip of the catheter to an external collection source at the distal end of the device.[3] The second lumen is for the operation of the inflation balloon, which anchors the catheter in place within the bladder. Coude—or bent—tipped catheters also exist as an alternative design to bypass obstructions and reduce pain in the curved urethras of males in the insertion process.[3] Transurethral catheterization—insertion of a catheter through the urethra—is the most common and generally, the safest method of indwelling catheterization, but other methods of urinary drainage such as suprapubic catheterization also exist.[3] Placement of a suprapubic catheter requires a surgical procedure, which has a low risk of bowel perforations and other associated morbidities[12] but also has higher reported levels of patient satisfaction.[12,13]

1.1.3 Elastomeric Catheter Materials

Polymers are a class of materials widely used to manufacture catheters and comprise long chains containing many repeating small subunits (monomers). The physical and mechanical properties of these materials can be tailored to specific applications, depending on the subunit type and fabrication method, leading them to be commonly used in medical applications.[14] One subgroup of polymeric materials is elastic polymers, otherwise known as elastomers. Elastomer chains are random coils connected with crosslinks, forming a polymer matrix.[15] The crosslinks can be achieved through the chemical crosslinking of polymeric chains together in the presence of a catalyst.[16] This is commonly accomplished through addition or condensation reaction chemistry.[16]

When a deforming force is applied to these materials, they can withstand extensive low-stress deformation and return to their original geometry once the deforming force is released, given no elastic (permanent) deformation has occurred.[14,16] As the force is applied, the chains uncoil and elongate, but the structure is retained due to crosslinking, and when the force is released, the chains recoil to their original

configuration[15]. These properties are aided by elastomers existing above their glass transition temperature (Tg). Below the Tg, materials are rigid solids, while above it, they can exist as a rubbery solid, leading to elastic rubber-like properties as there is sufficient thermal energy for increased chain mobility and flexibility.[14]

Urinary catheters are fabricated from many different elastomeric materials, such as latex, polyurethane, and polydimethylsiloxane (PDMS), commonly known as silicone.[4–6] Catheters, such as silicone-coated latex catheters, may comprise one or more of these materials to improve performance. However, due to many undesirable material properties[5] and allergic responses to materials such as latex,[4,5] silicone remains the preferred material[6] and is already used in a plethora of medical applications, such as contact lenses, implants, heart valves, and endoscopes.[4,5,17,18] This is due to desired material properties such as biocompatibility, low thrombogenicity, and enhanced chemical and thermal stability. Further, silicone materials exhibit higher resistance to kinking compared to latex[4] and are recommended by the Centers for Disease Control and Prevention (CDC) for patients with frequent catheter obstructions.[6]

1.1.3.1 Polydimethylsiloxane

The chemical structure of PDMS contains a silicone-oxygen chain backbone consisting of repeating monomers, with the letter n denoting the degree of polymerization, which is the number of repeat monomer units in a particular chain (Figure 1.3). Changing the degree of polymerization results in differences in the chain's molecular weight (MW).[19,20] Silicone fluids comprise lower MW and, therefore, shorter silicone chains, with their viscosity depending on the degree of polymerization. Alternatively, very high MW silicone chains are much longer and are used to fabricate elastomeric materials through chemical crosslinking processes.[16,21] Although many different elastomeric catheter materials have been developed and tested, the

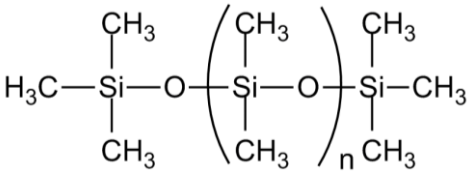

Figure 1.3. The chemical structure of silicone polymers. Photo credit: Gelest Inc.

most significant risk factor for infection remains the catheter's insertion, which places patients at an unavoidably higher risk of infection.[8]

1.1.4 CAUTI

Despite the prevalence of catheter usage to treat patients with abnormal bladder function, there exists significant risk with their use. There is an estimated three to seven percent risk of developing a catheter-associated urinary tract infection (CAUTI)—an infection of any of the components of the urinary system—per day of catheter use.[8] For patients catheterized over 30 days, this effectively guarantees the development of CAUTI. This heavily contributes to CAUTI being one of the most common hospital-acquired infections (HAIs), accounting for 40% of all hospital-acquired infections (HAIs)[3,4,8] and an estimated financial burden of $340–450 million annually in just the United States alone.[22,23] Per case, costs can range from $976–$10,197 depending on the type of insurance and severity of the infection.[24–27] In addition, over 100 million catheters are used annually globally, further contributing to this issue.[9] Inappropriate use and lack of awareness of catheters in patients also play a significant role. In one study, 31% of patients with an indwelling Foley catheter did not meet the proper criteria for needing it, and attending physicians were unaware of the catheterization of a patient 38% of the time.[9] Although the duration of catheterization is the most significant factor in the risk of developing CAUTI,[28] other risk factors contribute to the development of infection. Patient populations such as older adults, females, or those who already possess health conditions such as paralysis, cerebrovascular disease, and diabetes mellitus have an elevated risk of developing CAUTIs when catheterized.[29,30] Pathogens such as *Escherichia coli*, *Candida spp*, *Enterococcus spp*, *Pseudomonas aeruginosa*, and *Klebsiella spp* commonly cause CAUTI.[31]

1.1.5 Clinical Presentation and Diagnosis of CAUTI

Clinical presentation of CAUTI is fever, frequent or painful urination, tenderness in the area, and cloudiness or odor in the urine.[32,33] In older adults, CAUTI can cause behavioral changes or sudden mental decline due to infection that can manifest in confusion and deliriousness.[34] Asymptomatic infections are due to bacterial presence in the urine—otherwise known as bacteriuria—but fail to present symptoms, with one multicenter

study finding that ~90% of CAUTI patients had asymptomatic CAUTI.[30] Although not typically harmful, asymptomatic bacteriuria will often be unnecessarily treated with antibiotics, which can accelerate the evolution of multidrug-resistant organisms (MDROs) such as vancomycin-resistance *Enterococci* (VRE) and methicillin resistance *Staphylococcus aureus* (MRSA).[32,34–36] Critically, a summary of reported HAI data from U.S. healthcare facilities to the Healthcare Safety Network (NHSN) from 2011–2014 found that antibiotic-resistant pathogens were more often obtained from device-associated HAIs than from surgical site infections,[37] highlighting the risk of infection of device-associated MDROs.

As defined by the CDC, there are three main presentation criteria for diagnosing CAUTI: 1) the patient must have had the catheter inserted for at least 48 hours, 2) have $>10^5$ colony-forming units (CFUs) per mL of one microbial species present in their urine, and 3) have either fever, frequent or painful urination, or tenderness in the area.[33] Because of the nonspecific nature of many of these symptoms that may warrant urine culture testing, the diagnosis of CAUTI could be delayed, leading to more serious infections if not detected and treated in time. Severe infections can lead to pyelonephritis—kidney infection—due to pathogens traveling from the bladder to the kidneys, and from there, can result in bacteremia, or the presence of bacteria in the blood, which has been previously found to present in almost 50% of CAUTI cases in long term care facilities.[32] This type of infection is treated through an antibiotic regimen, the removal of the infected catheter, and all related supplies. If untreated, bacteremia can lead to conditions such as sepsis or endocarditis, which is the inflammation of the inner linings of the heart chambers, which increases mortality rates.[4] Regardless of the outcome, the risk of infection during catheterization remains high due to microbial colonization of catheter surfaces.

1.1.6 Biofilms

The presence of a urinary catheter allows for microbial colonization of its surfaces, creating an artificial pathway to the bladder,[36] and establishing favorable environments for initiating infection by common CAUTI-causing pathogens and other pathogens that would otherwise be unsuccessful.[31] These complex microbial communities are called biofilms, which are resistant to removal from the underlying material by

shear forces, antibiotic agents, and host immune responses, making them extremely difficult to treat. Furthermore, their formation can happen on hydrophilic and hydrophobic surfaces,[38] and even on minor surface defects on specially designed materials. Although it has been shown that the replacement of biofilm-contaminated indwelling catheters can improve patient outcomes,[39] it is challenging to prevent their formation without specifically designed surfaces.

When a catheter is first inserted into a patient, a conditioning film comprised of host proteins, electrolytes, and other molecules is released, coating the surface.[36] This enables planktonic—free-floating—bacteria to stick to this conditioning layer through either flagella or electrostatic or hydrophobic interactions.[23,36] Once adhered, the microbes begin secreting polysaccharides, proteins, and other organic molecules, creating an extracellular matrix and forming a biofilm, allowing further adherence of microbes.[36,40] As the biofilm grows, many mechanisms are employed to optimize survival. This can be seen through the formation of channel structures within the extracellular matrix that allows for nutrient and waste exchange,[36] the creation of pH gradients and altered microenvironments that can alter antibiotic function, along with the polymeric matrix itself limiting the diffusion of antibiotics into the biofilm.[38,40] Further, biofilms are more resistant to removal by shear forces,[36] and the altered microenvironment within biofilms allows microbes to withstand up to 1,000 times higher antibiotic concentrations than if they were planktonic.[23] Additionally, microbes within biofilms have also been found to manipulate gene regulation through quorum sensing—cell-to-cell communication of information—to create varying growth rates, with the more dormant pathogens closer to the underlying material being more protected.[38,40,41] Some organisms, such as *Proteus mirabilis* or *Pseudomonas aeruginosa*, release the enzyme urease that hydrolyzes urea in the urine to carbon dioxide and ammonium to cause the precipitation of minerals out of the urine by raising the pH, therefore creating crystalline biofilms for increased protection.[5,31] Once biofilms are fully matured, the top layers of biofilm can detach and further colonize surrounding areas.[23]

CAUTI-causing pathogens have various methods to avoid initial host immune responses. Studies with *E. coli* have demonstrated that many active microbes from biofilms invade and colonize umbrella cells—the stretchy bladder epithelial cells—to evade host immune responses.[42] This invasion process is initiated by

pathogenic type 1 pili filament proteins binding with umbrella cell mannose protein receptors. Once inside the umbrella cells, the *E. coli* suppresses cytokine production, which normally would initiate an immune response, alerting and recruiting nearby host immune cells.[43] As the immune system is not actively attacking infected host cells, the bacteria can replicate, forming bacterial reservoirs.[44] These reservoirs allow for subsequent reinfections and increased difficulty when treating them.

1.1.7 Fibrinogen

Catheterization induces mechanical trauma to the patient's urethra and bladder tissue, subsequently initiating immune and histological responses. Additionally, extended durations of catheterization are linked with continuous irritation and inflammation.[31] A host protein fibrinogen (Fg) is released in response to injury, which plays a critical role in the tissue repair process.[4,45,46] As seen in Figure 1.4, although Fg is released to initiate the healing of damaged host tissue and prevent infection, it can act as a scaffold for microbial attachment and subsequent biofilm formation, evidenced by the colocalization of the pathogen to Fg.[31,45] In the bloodstream, the enzyme thrombin converts the released soluble Fg proteins into fibrin, which causes the formation of clotting at the wound site.[47] It has been identified that Fg deposition is time-dependent and can start to coat catheter surfaces in as little as an hour, irrespective of the underlying catheter material.[48] In one study, increased microbial colonization was observed

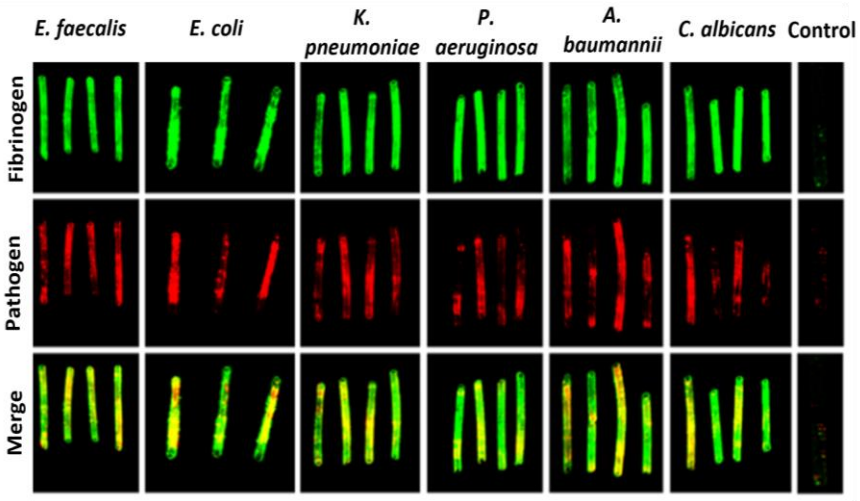

Figure 1.4. *In vivo* interactions between Fg and CAUTI pathogens.

Immunofluorescence images of the location of Fg (green) and respective pathogen (red) on urinary catheters implanted in mice. Unimplanted catheters were used as controls. Modified from Andersen *et al.* (2022).[48]

by common CAUTI-causing pathogens *Enterococcus faecalis, staphylococcus aureus*, and *Candida albicans* in the presence of Fg on indwelling catheters obtained from patients who underwent urologic procedures.[48] Moreover, many of these pathogens have evolved to have numerous Fg-binding domains,[45,46,48] highlighting the protein's importance in initiating biofilm formation and infection. Although Fg enhances pathogenic adherence to underlying materials, existing solutions for preventing CAUTI mainly aim to hinder pathogen attachment to underlying surfaces.

1.1.8 Existing Solutions

1.1.8.1 Catheterization Technique

It is estimated that up to 69% of CAUTI cases could be preventable, highlighting the room for improvement in catheterization criteria and technique.[49] Due to the increased risk of developing urinary tract infection (UTI) solely caused by catheter presence,[8] emphasis on CAUTI reduction has been placed on limiting the duration of catheterization and use of intermittent rather than indwelling catheters if possible.[6,7] For intermittent catheterization, using catheters with properly lubricated surfaces can assist in reducing mechanical damage to host tissue[50] and, therefore, Fg release.[4,46,48]

Ensuring proper hygienic techniques throughout the insertion and handling process during catheterization remains paramount. Approximately 34% of CAUTIs are caused by the transmission of exogenous pathogens to catheter surfaces due to improper aseptic insertion techniques.[7] Proper techniques include using sterile materials and aseptic insertion techniques and replacing all materials if there is leakage in the closed-loop drainage system.[6] Moreover, best practices, such as properly placing the urine collection bag below the bladder level and above the floor, will prevent the backflow of potentially infected urine from the collection bag into the catheter.[7]

1.1.8.2 Polymeric Coatings

Polytetrafluoroethylene (PTFE), otherwise known as Teflon, are commercially manufactured catheters that provide a low coefficient of friction to reduce biofilm formation.[4] PTFE-coated catheters have been used

as control materials in clinical trials investigating various coating efficacies, showing their clinical use.[28] However, studies have shown that after 14 days of use, Teflon-coated catheters were found to have more blockages and heavy encrustation than all-silicone catheters, leading to silicone being recommended for extended durations.[51] Other studies have asserted that non-coated materials or hydrophilic coatings, such as hydrogels, are more effective at reducing CAUTI than PTFE.[4]

Hydrogels are crosslinked polymeric structures that retain large amounts of water within their matrix once swollen without dissolving.[52,53] Crosslinks can be formed through physical methods such as the entanglement of polymer chains, hydrogen bonding, ionic interactions, or through chemical crosslinking of chains using a crosslinking agent.[53] Catheters are often fabricated with hydrogel coatings to diminish mechanical trauma compared to silicone or latex catheters by the formation of a smooth hydration layer,[4,50,52,54] and the layer can also operate as a barrier to prevent the adsorption of host proteins.[4,52] Kazmierska and others found that planktonic *P. mirabilis* could adhere in higher numbers in the presence of a hydrogel layer in an *in vitro* bladder model compared to all-silicone.[55] Further, a small clinical study of 77 patients found that hydrogel-coated silicone or silicone-coated latex catheters were associated with higher inflammatory reactions than all-silicone control during short-term catheterization.[54] To enhance the anti-biofilm performance of catheter materials, investigation into embedded antimicrobials such as metals and antibiotics for sustained release has been conducted.[4,5,56]

1.1.8.3 Antibiotics

Antibiotics inhibit or prevent biofilm growth at low concentrations through various mechanisms, with many offering higher efficacy than other types of coatings.[5] One of the most popular and commercially available antibiotics impregnated into catheter materials is nitrofurazone.[4,5,56] Nitrofurazone inhibits DNA replication, preventing further growth of pathogens in contact with the surface and surrounding areas.[4,5,56] When tested *in vitro*, nitrofurazone-impregnated silicone catheters significantly reduced *E. coli* and *E. faecalis* for up to five days compared to unimpregnated controls when incubated in a liquid medium.[50] However, when used clinically, lower effectiveness and higher levels of patient discomfort are reported.[57,58]

Further, the Food and Drug Administration (FDA)—the regulating body for all medical devices and pharmaceuticals in the United States—banned its use as a topical antiseptic for over-the-counter use due to carcinogenic side effects, which has slowed its use.[4,5,56] Nitrofural use on catheters was not barred, so it remains available for clinical use but is a less desirable solution.[4] Catheters impregnated with other common antibiotics such as gentamicin, fluoroquinolones, and chlorohexidine have displayed promise in reducing pathogenic colonization *in vitro*, but clinical trials for human use have yet to be conducted.[4,56]

1.1.8.4 Silver Alloy

Another heavily used antimicrobial coating is silver ions, which induce oxidative stress in bacteria through the initiation of membrane and protein dysfunction.[4,5,56] However, the effectiveness of silver is heavily debated as there have been mixed results from both *in vitro* and clinical studies investigating the efficacy of silver and hydrogel (SAH)-coated catheters. In a seven-hospital cohort study conducted by Lederer and colleagues (2014), it was found that there was a 58% reduction in CAUTI occurrences by NHSN definition when compared to the currently used catheters (most commonly hydrogel-coated latex or non-coated silicone catheters).[28] A randomized crossover study found that SAH-coated latex catheters reduced the risk of infection by up to 32% and could offer estimated savings of $14,000–$573,000, not adjusted for inflation.[59]

Other studies have produced contrasting findings about the efficacy of SAH in reducing CAUTI. *In vitro* experimentation conducted by Desai and colleagues demonstrated that there were no significant reductions in *E. faecalis* and *E. coli* adherence when using commercially available silver-coated catheters.[50] A separate multicenter randomized control trial encompassing ~6,300 patients compared the effectiveness of SAH-coated catheters to PTFE controls for short-term catheterization and found no significant differences.[57,58] Additional conclusions were that using catheters would not be a cost-effective solution to prevent CAUTI.[60] Further, coating both internal and external surfaces with SAH or silver alloy layer can depend on the manufacturer and model of the catheter,[50] which could contribute to its mixed effectiveness. Although most

infections occur from bacteria accessing extraluminal surfaces,[7] pathogens colonizing intraluminal surfaces could be sheltered from the effects of SAH coatings on certain catheter models.

Due to conflicting results of commercially available coatings in both *in vitro* and *in vivo* studies, more work must be done to enhance antibiofilm performance further. As many biofilms may tolerate elevated concentrations of antibiotics, compounded by the growing risk of antibiotic resistance, moving away from antibiotic-reliant solutions would be beneficial. Moreover, as the deposition of Fg on catheter surfaces is not always uniform,[46,48] and the adsorption of other host proteins can occur,[45] pathogens can be shielded from the biofilm formation inhibiting effects of the antimicrobial-releasing surfaces.[61,62] Therefore, successful catheter materials and coatings must be designed to prevent the adhesion of the initial proteins, which in turn impedes biofilm formation.

1.2 Liquid-Infused Polymers (LIPs)

To successfully prevent biofilm formation, an antifouling coating must repel the biofilm conditioning layer[5,63] and host proteins.[45] One such method to accomplish this is through liquid-infused polymers, where polymers are exposed to excess amounts of a chemically similar liquid, resulting in full saturation that can shed off surface contaminants in various conditions (Figure 1.5).[64–67] The liquid is associated with the underlying substrate through van der Waals forces, and in substrates with rough surfaces, capillary action, resulting in low-force liquid adhesion to the substrate.[66,68] With this method, the liquid must have a higher affinity for the

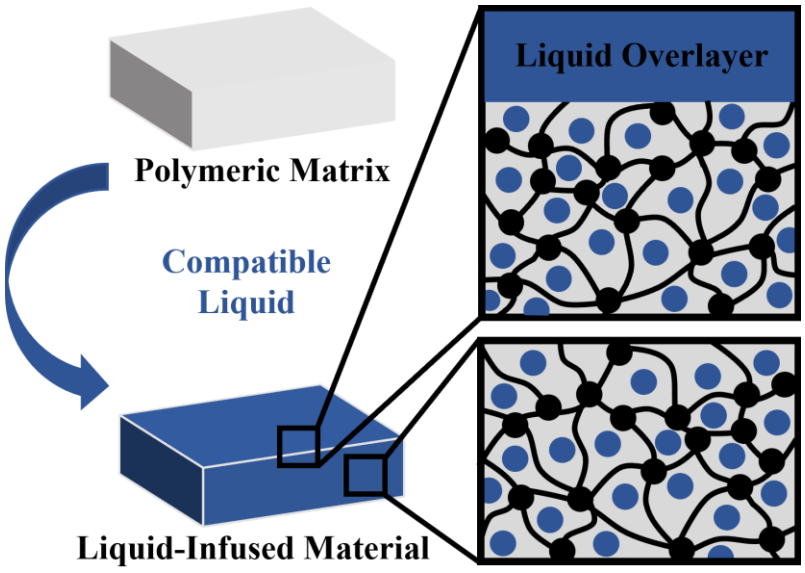

Figure 1.5. Schematic of the infusion of a polymeric matrix with a compatible liquid.

substrate rather than the contaminant to retain the protective layer.[68,69] Medically relevant materials such as PDMS and silicone oils have proven effective antifouling materials against biological materials *in vitro*, such as proteins and relevant CAUTI-causing pathogens,[45,64,66,67] and the controllable release of mammalian cell sheets.[70]

1.2.1 Diffusion of Silicone Oil into PDMS

As silicone oil is a solvent for PDMS, the swelling of the material due to silicone oil absorption into the polymeric matrix can be modeled as the balance between entropy and enthalpy within the system, as explained by the Flory-Rehner theory.[71,72] Introducing the compatible solvent induces polymer chain elongation because the chains maximize polymer-solvent interactions, reducing the number of possible configurations.[73] This causes a reduction of the entropy (disorder) within the system. Conversely, the entropy of the solvent mixing within the polymeric network increases as it is imbibed within the elastomer. Complete infusion, indicated by a plateau in mass as no more silicone oil can be absorbed, results from the equalization of the entropies.[71–73] As there is a high chemical similarity between silicone oil and the elastomeric matrix, the enthalpic differences between the two materials are not expected to impact the system considerably.[73]

Once placed in the bath of silicone oil, a high concentration gradient is created between the high concentration of silicone oil at the boundary of the elastomeric matrix, acting as the driving force of diffusion of the oil into the matrix to achieve equilibrium. The rate of change of the oil concentration within the matrix can be described through Fick's second law of diffusion.[74] The swelling of PDMS with silicone oil can be interpreted through poroelasticity theory and Darcy's law, which describes fluid flow through a porous material.[73,75] In these conditions, all increases in the volume of the PDMS matrix can be attributed to changes in the concentration of solvent within the matrix.[73] This was demonstrated by Sotiri and colleagues, who found that the extent and rate of oil diffusion into the bulk depended on the crosslinking density within the network and the viscosity of the infusing oil.[73] PDMS elastomers with lower crosslinking ratios (i.e., larger spaces between crosslinks and the ability to expand further) infused with low-viscosity

silicone oil were shown to have the largest mass increases in shorter timeframes. Lower-viscosity solutions diffuse at higher rates due to the smaller molecular chains than those with higher viscosity. However, regardless of the crosslinking ratio or viscosity of the oil, there reaches a point where the matrix can no longer absorb oil, indicating equilibrium.

1.2.2 *In Vivo* Testing of Liquid-Infused Catheters

In vitro testing allows for initial meaningful data collection, but the complexity of *in vivo* environments is hard to replicate. For this reason, Andersen and colleagues (2022) tested the effectiveness of liquid-infused silicone tubing infused with 20 centistokes (cSt) silicone oil in resisting pathogenic adherence to catheter surfaces through *in vivo* experimentation in a mouse model of CAUTI.[45] Mice were infected with one of six common CAUTI-causing pathogens before being catheterized with either unmodified or liquid-infused silicone (LIS) catheters for 24 hours, at which point organs such as the bladder, kidneys, spleen, and heart were harvested to quantify the extent of dissemination of the pathogen to the organ (Figure 1.6). Critically, there was a significant reduction in the number of pathogen CFUs found in the bladder tissue and the catheter surface in the liquid-infused group compared to the unmodified controls through limited Fg and host protein deposition. Additionally, many pathogen-dependent reductions in CFU counts in other harvested organs occurred.

Through hematoxylin and eosin (H&E) staining—which can be used to identify the presence of inflammation in tissue samples—they found that liquid-infused catheters did not further enhance the inflammation of mouse bladder tissue. In half of the pathogenic infection conditions, there was reduced inflammation.[45] Despite preclinical success in mice, clinical trial data on the safety of low-viscosity silicone oil in humans is still needed.

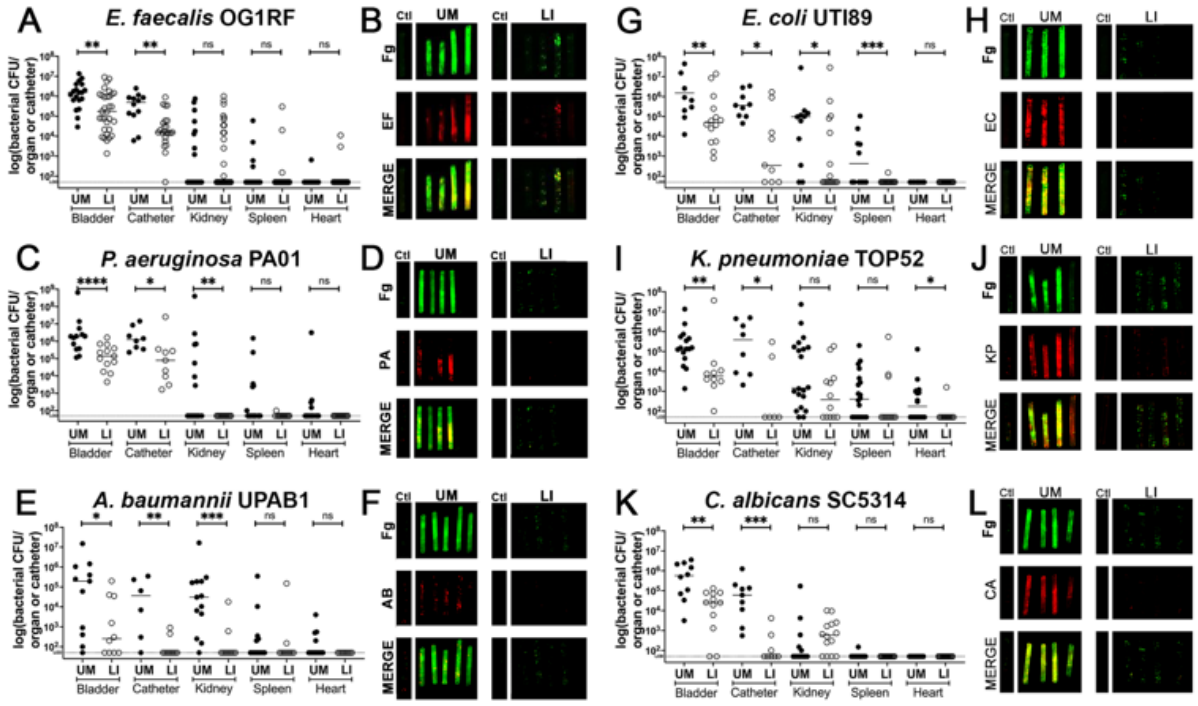

Figure 1.6. Liquid-infused treatments reduce microbial presence by limiting Fg deposition in catheterized mice.

(A, C, E, G, I, K) Organ and catheter CFUs from unmodified (closed circles) or liquid-infused silicone (LI) (open circles) catheterized mice infected with one of six common CAUTI-causing pathogens. (B, D, F, H, J, L) Images of Fg (green) and respective pathogen (red) and merged comparison of UM and LI catheters. Figure credit: Andersen *et al.* (2022).[48]

1.2.3 Potential Health Impacts of Silicone Oil

Although Andersen and colleagues (2022) found promising results that liquid-infused catheters were able to reduce host protein and bacterial adhesion to control infection without increasing inflammation in host tissue,[45] concerns remain related to the use of silicone oil in the human body as it is a foreign liquid.[76–78] *In vivo* studies have found that silicone oil can act as a potential immunological adjuvant by readily forming complexes with proteins due to the large surface area of the small silicone oil droplets, which can subsequently elevate the levels of antidrug antibodies in plasma.[76,77,79,80] Additionally, it has been reported that granulomas—hardened groups of immune cells—have formed in response to silicone oil injections.[81]

Silicone oils are approved for use in medical applications such as lubricants and ocular tamponades.[78,81–83] Outside the body, it is commonly used for plungers of commercially available disposable syringes. It is estimated that 0.6–1 mg/mL of silicone oil is applied by spray coating of baked-on methods to coat the barrels.[79,84] As many drug formulations are transported and stored in disposable syringes, silicone oil will inevitably leach off of the barrel into the syringe contents.[79] If agitated through methods mimicking excess dropping, levels of silicone oil released could be up to 0.16 (±0.05) mg/mL during injection.[76] This suggests that some amount of silicone oil in the blood is tolerable, but the degree to how much is absorbed and any immune reaction depends on factors such as the molecular weight of the oil.[19]

The FDA has approved highly viscous silicone oils (ranging from 1,000–5,500 cSt) for use in humans as ocular tamponades (e.g., Adatosil-5000 and Silikon 1000) to treat diseases such as retinal detachment or diabetic retinopathy.[81–83] However, even with these high-viscosity oils, there are still reports of microemulsions of silicone oil[82] or cataracts[83] within treated eyes. In one study of nine patients with either 1,300 or 5,500 cSt silicone oil within their eye(s) for durations ranging from one month to two years, emulsions with a median diameter of 1.1-1.9 μm were found in six patients.[82] This highlights that even at high viscosities, silicone oil in the body can emulsify, which could cause adverse effects.

Outside of retinal use, FDA-approved uses of silicone oil with urinary catheters exist today, although the viscosity is unknown. CompactCath produces a single-use silicone oil-coated polyvinyl chloride (PVC) intermittent urinary catheter to reduce insertion friction. This suggests silicone oil is a promising catheter lubricant material as it is already approved for use in patients who use intermittent catheterization multiple times daily and likely does not harm urinary tissue. However, this is different from the extended contact silicone oil would have with host tissue if it were on the surface of an indwelling urinary catheter. For this reason, more data is needed to ensure patient safety and translate this technology for human use.

Chapter 2

TECHNOLOGY TRANSFER AND ENTREPRENEURIAL TRAINING

Technology transfer and entrepreneurial training programs are in place to help researchers translate technology from a laboratory to a consumer—a process that can be difficult if done without training or additional assistance. These programs teach researchers and scientists about commercialization by aiding in developing their business model through market analysis, customer discovery, and intellectual property. With new training in an evidence-based approach, these programs better position researchers for more successful outcomes in commercializing their products or services. This work explored entrepreneurial training through the University of Maine's Innovation Core (I-Corps) program sponsored by the National Science Foundation (NSF). The program allowed for analysis of components of the business model canvas, such as identifying customer segments and relationships and considering aspects such as key partners, activities, resources, cost structures, revenue streams, and channels for the new technology. Through this program, 10 interviews were conducted with individuals in person or on Zoom to better comprehend the landscape regarding urinary catheters, their use in medical facilities, and current shortcomings with existing devices. All individuals interviewed were associated in some capacity with either the Northern Light Healthcare system or the Eastern Maine Medical Center facility in Bangor, Maine. No explicit mention of the new technology was made during the interviews, and a list of general questions asked during the interviews can be found in Appendix A. All information learned and training completed was used to better prepare the technology for commercialization. The technology was called protein resistance optimized (PRO)-Catheter for the duration of the program.

2.1 Introduction Summary of Proposed Technology

The I-Corps training was completed to enhance the commercialization ability of PRO-Catheter by pivoting development if necessary to bridge gaps left by current solutions. The fundamental PRO-Catheter technology consists of a commercially manufactured all-silicone catheter and the infusion of this device with silicone oil, creating a slippery exterior surface and inner lumen. Adding the slippery layer on the

silicone surfaces would lower incidences of CAUTI due to the reduction of Fg and pathogens on catheter surfaces.[45,62]

2.2 Value Propositions

Customers are unlikely to adopt the new technology without value propositions as they cannot compare the benefits with those offered by the existing solutions. Talking with clinicians and staff involved with catheter usage allowed for properly identifying value propositions. A recurring theme across many of the interviews conducted during customer discovery was that a significant benefit of adopting new technologies would be compatibility with existing materials, procedures, or systems. One component of the CAUTI mouse model study conducted by Andersen *et al.* (2022) was testing all-silicone catheters manufactured by Bard and Dover that were fully infused with silicone oil and subsequently incubated with Fg *in vitro*. It was found that Fg reduction was reduced by ~90% in Dover catheters and ~99.99% in Bard catheters.[45] This demonstrated compatibility with commercially manufactured catheters. Furthermore, the development of CAUTI has been linked with an increased length of stay in hospitals, ranging from two to four days,[6] which incurs extra costs for the patient and can be emotionally and mentally taxing for both patients and staff caring for them. With the reduction in the amount of Fg to catheter surfaces, we predicted there would be less risk of infection and decreased length of stay related to CAUTI. To further assess compatibility, three brands of indwelling urinary catheters were investigated: Bard, Medline, and Dover across 14, 16, and 18 Fr sizes, which cost anywhere from $3.77–$12.5 per catheter to obtain. Preliminary testing of fully infusing these catheters with 20 cSt silicone oil resulted in mass increases of 6.6–9 grams (g), leading to treatment prices ranging from $0.33–$0.45.

2.3 Key Partners

Key partners are partnerships with people or entities that can further enhance the success of the proposed new technology and help it succeed in the market. Key partners identified in this work were catheter manufacturers and clinicians or medical professionals. A utility patent—a patent that protects a novel functionality of a given process or invention—is essential to the technology's survival. This has already

been obtained, enabling the licensing of the protected process to a manufacturer and ensuring that no other entity, such as a competitor in the market, can use this process. The next key partner was a medical manufacturing company. Having a partner with existing infrastructure to fabricate urinary catheters and existing FDA approval to market them would be extremely difficult to emulate if we manufacture the new products ourselves. As these companies have existing submissions to the FDA for their products, if they add silicone oil to the product, they could modify their existing FDA submission. As we are already treating commercial urinary catheters, the manufacturing partner could be able to treat catheters before packaging and distribution. Lastly, having the support or endorsement of physicians and nurses to recommend the new technology to patients, hospital materials staff, and insurance companies would be immensely helpful in the mass adoption of the new technology.

2.4 Channels

Channels are the distribution pathways allowing a product to reach customers. Typical channels could be through distributors or the Internet. In this case, selling the product to healthcare facilities could be accomplished through medical device distributors, hospital sales representatives, attending medical conferences, or online ads. Through customer discovery, a specific channel of importance was identified. Group purchasing organizations (GPOs) are collections of large vendors or distributors that buy medical supplies in vast volumes, allowing them to negotiate pricing with manufacturers and other distributors. A contractual agreement between a healthcare facility and a GPO outlines certain products to supply, with discounted pricing on specific items stated in the contract. Facilities can obtain supplies not covered in the contract from the GPO, but not at preferred pricing. Typically, facilities try to order a certain percentage (upwards of 80%) covered by the contract to receive a rebate on purchased supplies. For products that are not covered in the GPO contract, they can be ordered through the gray market. This is a collection of reputable companies outside of the GPO that provide FDA-approved products to facilities.

As new technology is constantly being developed to benefit patients and reduce costs for facilities, there are ways to get new equipment or supplies ordered for facility-wide use through the value analysis

department, which uses a website called Lumere. This website gives the ability for staff such as clinicians, nurses, or engineers to submit a request about a product they have heard about (e.g., from other previously mentioned channels), giving the value analysis department information on things such as cost and safety. Using Lumere, the value analysis department can better evaluate new products effectively. The goal is to save money when purchasing medical supplies, but products that offer enhanced quality or reusability are far more likely to be bought. Due to this information, it is expected that getting this product to be stocked by a GPO, demonstrating its effectiveness and safety, and having demand from healthcare providers would result in overall profitability.

2.5 Cost Structure and Revenue Streams

Identifying the cost structure is crucial to the potential success of a new technology intended for commercialization. PRO-Catheter has been proven successful at reducing CAUTI infections in mice.[45] However, significant hurdles must be overcome for human use, each coming with its own costs. As silicone tubing was used in mice, time and money must be put towards the research and development to quantify further how the liquid infusion alters the functionality of the commercial catheter post-infusion with silicone oil. Further costs associated with preclinical benchtop testing are further exploring the manufacturing, sterilization, and compliant packaging of the materials at pilot scale or large scale. Ideally, this would be accomplished by a medical manufacturing partner. To demonstrate PRO-Catheter's effectiveness further than in preclinical mice data, a human clinical trial must be conducted to compare the rates of CAUTI in PRO-Catheter devices and the gold standard all-silicone Foley catheters. Once data is collected, an application must be filed with the FDA. The utility patent for the technology's manufacturing process could be licensed to a commercial manufacturer to enable the product to reach a broader audience. Revenue streams generated from PRO-Catheter would be through medical distributors, vendors, and GPOs.

2.6 Customer Segments

Customer segments are the specific groups of customers most likely to adopt your new product and benefit from it the most. Three primary customer segments were defined through customer discovery: end users,

decision-makers, and payers. The end users were identified to be nurses, physicians, and caregivers of elderly patients. These are the people who are informed and are actively deciding if one product is inherently better due to its level of safety and effectiveness, rather than the patient who is most likely being told by a clinician or caregiver which brand or size catheter to use for treatment. Additionally, at an administrative level in healthcare facilities, hospital administrators need to make cost-based decisions on medical products based on a variety of data. If using PRO-Catheters rather than the currently used model is demonstrated to reduce rates of infection and therefore incurred costs on patients and healthcare facilities alike,[24,25,27] in theory, it is more likely to be adopted. Furthermore, if this can be proven, it would be more likely to be adopted by the payers, which are insurance companies.

2.7 Customer Relationships

An essential part of any successful business model relies on continually obtaining new customers, but importantly, working to retain existing ones.[85] This depends on developing relationships with customers and actively engaging with them. The feedback received by participants and medical staff in future clinical trials and eventually by having a dedicated technical support team to field all customer questions would make the retention of customers identified in the customer segment section easier.

2.8 Summary

After finishing the entrepreneurial training, key activities were identified, such that completion would allow for the commercial viability of the PRO-Catheter technology. These activities are further investigation of the mechanical and potential functionality changes caused by the infusion. A complete understanding of the physical properties would allow for the demonstration of the efficacy of the technology and enable licensing to a medical manufacturer with existing infrastructure and a significantly larger available budget if interested. Further, this would aid in facilitating clinical trials. To help achieve these goals, the quantification of parameter changes of commercial catheters infused with silicone oil, determination of how much silicone oil remains on the surface, and assessing the performance of these devices through standardized testing were conducted.

Chapter 3

DEVELOPMENT AND CHARACTERIZATION OF LIQUID-INFUSED SILICONES

Due to the success seen *in vivo* through reductions in host protein and microbe adherence to liquid-infused silicones,[45] more information on how the infusion process influences the bulk material is needed. Previous studies have shown that the infusion of silicone oil into PDMS is time-dependent, and the reduction of properties indicative of material stiffness in infused PDMS depends on both the crosslinking ratio of the PDMS matrix[73,86,87] and the viscosity of the infusing liquid.[62,73] In PDMS squares infused with silicone oil, elastomers with higher base-to-crosslinking ratios swelled less as there were more crosslinking sites, and conversely, lower crosslinking ratios provided higher swelling ratios.[73,86] Further, fully infusing PDMS with silicone oil generates a liquid overlayer on the surface.[62,64–66,73] We aim to enhance patient comfort and usability by introducing a liquid-infused coating on various sizes of catheters. However, further research is crucial to ensure the safety and integrity of these infused materials.

This chapter investigates the amount of liquid on the surface of liquid-infused PDMS, how the time-dependent infusion process alters commercial catheters, and the mechanical properties of the PDMS that comprise them. For the successful approval and subsequent use of liquid-infused catheters in humans, it is imperative to understand the extent of material changes caused by adding the liquid to the polymeric matrix. This includes obtaining changes in crucial mechanical properties and quantifying the presence of oil on catheter surfaces. Such understanding will not only ensure the device's safety but also allow for enhanced performance.

3.1 Materials and Methods

3.1.1 Commercial Catheter Infusion

Bardia All-Silicone Two-Way catheters (CR Bard), SelectSilicone 100% Silicone Foley catheters (Medline Industries), and Dover Adult Silicone 2-way Foley catheters (Cardinal Health) were obtained in sizes ranging from 14-18 Fr. Entire catheters were submerged in a bath of 20 centistokes (cSt) trimethoxy-terminated silicone oil (Gelest, DMS-T12) for at least six days to achieve full infusion, indicated by a

plateau in the change in mass of the sample. Changes in parameters such as mass, length, and inner and outer diameter were recorded before and during infusion. A subset of catheters had two centimeters (cm) sections cut out of the shaft region to record the inner diameter throughout the infusion accurately. To quantify parameter changes in silicone-coated latex catheters, Bardia Silicone-Elastomer Coated Latex Foley catheters (CR Bard) were subjected to the same experimental procedure as the all-silicone catheters.

3.1.2 Polydimethylsiloxane Stock Preparation and Silicone Oil Infusion

Sylgard 184 silicone elastomer (Dow Corning) was used for all PDMS fabrication. The elastomer base was mixed with the platinum curing agent at a 10:1 ratio. The mixture was then mixed with a desktop planetary mixer (ARE-310, Thinky Corporation) at 2000 revolutions per minute (rpm) for one minute, followed by 2200 rpm for an additional minute. The PDMS mixture was poured into its desired mold and placed into a vacuum chamber to degas for at least 60 minutes or until all bubbles had disappeared. The mold was then put into a convection oven (Isotemp, Fisher Scientific) at 70 °C overnight to facilitate curing. Once cured, the PDMS was removed from the mold, and the mass of the sample was recorded.

PDMS samples were submerged in a 20 cSt silicone oil bath and were removed periodically; excess silicone oil was first allowed to drain by holding the sample vertically for 30 seconds or until excess oil had dripped off. Additional oil was dabbed off the surfaces using a cellulosic wipe (Kim-wipe, Kimberly Clark Corporation) and subsequently weighed. For full infusion, the samples were left in oil until the mass plateaued, indicating full infusion of the material. For partial infusion, samples were removed at predefined time points.

3.1.3 Infusion of Fabricated Test Samples

For reasons outlined in the coming sections, many experiments could not successfully be carried out without fabricating PDMS samples due to commercial catheter limitations. Fabrication of fully infused PDMS samples was obtained as described in section 3.1.2. This yields the maximum swelling ratio of the material, Q_{max}, which was determined through the formula:

$$Q_{max} = \frac{m_s}{m_i} \quad (1)$$

where m_i is the initial dry weight of the sample, m_s is the swollen mass of the sample once the change in mass of the plateaus, indicating complete infusion.[62,87] Once the maximum level of infusion is determined, calculations for the infusion duration to reach the desired partial infusion can be conducted. This is accomplished through the formula:

$$Q = \frac{m_t}{m_i} \quad (2)$$

with m_t representing the mass recorded at a given point in time (t) after the infusion has started and m_i being the initial dry weight of the sample. Once obtained, Q is entered into the equation below to obtain an infusion percentage ranging from 0–100% infused:

$$\text{Infusion percentage (\%)} = \frac{(Q-1)}{(Q_{max}-1)} * 100 \quad (3)$$

For each experiment run, Q_{max} was calculated to adequately estimate the time needed to obtain the desired infusion percentages of 0, 25, 50, 75, and 100% infused.

3.1.4 Confocal Imaging of Infused PDMS Samples

3.1.4.1 Sample Preparation

Fluorescent PDMS stock was created by dissolving 850 µg of BODIPDY FL alkyne dye (Lumiprobe) in 10 mL of dichloromethane (Fisher Scientific) and mixed with 100 g of Sylard 184 base agent using the planetary mixing procedure described previously. The stock was placed into a vacuum chamber and degassed overnight. Following this, 10 g of Sylgard 184 curing agent was added to the stock mixture and mixed using the planetary mixer. Aliquots of 0.9 milliliters (mL) were transferred to 20 millimeters (mm) x 20 mm x 2.5 mm square depressions in a mold master and placed in a vacuum chamber for two hours to degas and then in an oven at 70 °C overnight to facilitate curing. Fluorescent silicone oil was prepared by adding nine milligrams (mg) of pyrromethene 597-8C9 (Exciton-Luxottica) to 100 mL of 20 cSt silicone

oil and mixing it in the planetary mixer. The solution was then filtered using a 0.22 micrometer (μm) nylon syringe filter (Thermo Scientific) to remove particulates before infusion. Partial and full infusions were conducted following the procedures previously described. Samples that reached the desired partial infusion percentage were removed from the oil bath and sat for at least 48 hours to allow for equilibration of oil within the sample. Finally, imaging was performed on a Nikon AXR Confocal Point Scanning Microscope (Nikon Instruments) using a PLAN APO λD 10x/0.45 NA objective (Nikon Instruments), with a step size of 4.4 μm and a pinhole size of 41.6 μm. Fully infused samples were titled vertically to remove excess oil from the surface; blotted samples had the oil overlayer mechanically stripped with a cellulosic wipe.

3.1.4.2 Oil Overlayer Measurement

After imaging, the acquired ND2 image files were opened in ImageJ software to determine the oil overlayer height. The two channels were merged, creating a Z-stack, leading to an overlayed composite image in the XZ direction. Images were saved as TIFF file types, which preserved the scale of the image in both pixels and microns for further analysis. Once reopened, the interface of each image zoomed in to 200%. At pixel location x=100, a vertical line was drawn from the top of the bulk material to the top of the oil layer. The analyze function was then used to record the length of the line, representing the height of the oil layer. As it was difficult to accurately distinguish the interface between the two materials in oil overlayers with heights less than five μm, the limit of detection (LOD) was set to five μm. Although this is higher than the axial resolution limit of confocal microscopy (0.5 μm), oil overlayer heights below this threshold could prove inaccurate and were thus recorded as five μm. This process was repeated for pixel locations X=256, 512, 772, and 924 for each image to obtain the average oil overlayer height for all images and samples.

3.1.4.3 Total Mass of Silicone Oil Present on Catheter Surfaces

The experimentally determined values for the outer diameter and length of a fully infused 14 Fr catheter and the measured oil overlayer heights were input into the equation for a hollow cylinder to obtain the volume of silicone oil present on the surface:

$$V = \pi(R^2 - r^2)h \quad (4)$$

Where R is the radius of the silicone oil overlayer plus the catheter outer diameter, r is the catheter outer diameter, h is the length of the catheter shaft region, and V represents the total volume of silicone oil present on the surface. Once the volume was obtained, the density of silicone oil was used to convert to the mass of oil on the surface:

$$\rho = \frac{m}{V} \quad (5)$$

Where ρ is the density of 20 cSt silicone oil (0.95 g/mL), and V is the volume obtained from the previous equation, yielding the final mass of silicone oil. The values were then converted from grams (g) to both mg and μg.

3.1.4.4 Calculation of Mean Gray Value

The TIFF files were opened in ImageJ and converted to 8-bit greyscale, assigning the pixel values from 0 (black) to 255 (white). The mean gray value (MGV) is the average pixel value in a given measurement area of pixels. A 400 x 80-pixel window starting at locations X=312 and Y=85 was used to standardize the measurement area. If heterogeneity in the bulk color due to surface defects was present in the measurement window, the starting pixel locations were adjusted to achieve homogeneity in bulk material appearance. Recording the heterogeneity would artificially decrease the mean gray value for each image and, therefore, was not included in the analysis.

3.1.5 3D Printing

To manufacture various 3D structures, SolidWorks 2024 (Dassault Systemes), a computer-aided design (CAD) software, was used to design the desired 3D part designs as part files. These part files were converted to stereolithography (STL) file formats and imported into PrusaSlicer Version 2.7.3 (Prusa Research) to convert the STL file into G-code, a numerical control language that a 3D printer can read. This takes in the 3D object and user-input settings and turns them into a series of commands for a 3D printer. For the printing

process, a Prusa MK3S+ (Prusa Research) fused deposition modeling (FDM) 3D printer was used to heat and extrude a thermoplastic filament layer by layer to create a 3D object. For objects printed, acrylonitrile styrene acrylate (ASA) filament (Overture) was used with a nozzle temperature of 260 °C and a build plate temperature of 110 °C. The layer height was 0.05 mm, and the infill percentage was 50% at a gyroid infill pattern. Due to the need for an elevated ambient temperature and the need to reduce any potential air drafts when printing with ASA, an enclosure was used.

3.1.6 Mechanical Testing

3.1.6.1 Tensile Testing

PDMS test specimens were prepared following the stock preparation procedure described in section 3.1.2. The PDMS mixture was then poured into ASTM D412 (2021): Test Methods for Vulcanized Rubber and Thermoplastic Elastomers-Tension type C-compliant 3D printed molds and degassed for at least two hours. Samples were then cured overnight at 70 °C, removed from the mold, and either kept as controls or infused with silicone oil in an oil bath. Partially infused samples were removed from the oil bath at set time points and sat for at least six days to allow for equilibration of oil in the sample before testing. Before testing, all samples infused with silicone oil had excess oil removed from the surface of the specimen. They were then affixed to the grips of a Criterion Model 43 tensile testing machine (MTS systems). The crosshead velocity was 25 mm/minute, a five-kilonewton (kN) load cell was used, and all test samples were subjected to a standardized pre-load of 0.44 newtons (N) to ensure uniformity of conditions across each test specimen. Average testing conditions were 19.8 °C and 61% relative humidity (RH).

3.1.6.2 Shore OO Hardness Testing

To prepare samples, approximately 12.4 g of PDMS was poured into 60 mm x 15 mm circular Petri dishes **(**Fisher Scientific**)** and cured following the procedure outlined in section 3.1.2 before being removed from the mold and placed in a silicone oil bath. Samples that reached the desired percentages of partial infusion were removed from the oil bath and sat for at least 14 days to allow for equilibration of oil within the sample before measuring the hardness. Testing methodologies and data collection were consistent with ASTM

D2240-15: Standard Test Method for Rubber Property-Durometer Hardness (2021) to determine the hardness values of a material. For each infusion condition, five samples were tested in five predetermined locations per sample, consistent across tested samples. All measurements were taken within one to two seconds after full indentation, as relaxation of the polymeric material can occur after five seconds of indentation.[88] Durometer measurements were taken with Shore OO (1600-OO, Rex Gauge Company) and Shore A (1600-A, Rex Gauge Company) handheld durometers. The average testing conditions were 21.5 °C and 32% RH.

3.1.7 Statistical Analysis

Statistical analysis of data was conducted using GraphPad Prism, Version 10 (GraphPad Software). The statistical significance of experiments was tested using Mann-Whitney U or Analysis of Variance (ANOVA) tests. Significance values are: * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, **** = $p< 0.0001$.

3.2 Results and Discussion

3.2.1 Commercial Catheter Characterization

Many different factors could influence the ability of a commercially manufactured all-silicone catheter to absorb silicone oil. Each company may have a different ratio of base to curing agent as well as the choice of specific silicone rubber choice (i.e., platinum or peroxide cured rubber) for their respective catheter, which could play a role in any potential differences in the absorption of silicone oil into the bulk material through altering the extent of swelling.[71,72,89] Additionally, as recipes for each company's respective catheters are trade secrets, it is unknown if the ratio of silicone rubber to filler materials, such as reinforcing or antiaging agents, is consistent across brands.[90,91] For this reason, commercially available all-silicone urinary catheters were infused with 20 cSt silicone oil, the viscosity used in the mouse CAUTI model study.[45] Parameters such as mass, inner and outer diameter, and length were then quantified—all of which are important as these devices are intended for use in a patient. Previous literature has found that increasing catheter outer diameter and reducing length resulted in faster drainage times. However, once the outer diameter exceeds 18 Fr (~6 mm), there are diminishing drainage levels concerning the increase in outer

diameter[13]. Due to the time-dependent increase in parameters such as inner and outer diameter and length, it is crucial to determine what initial materials to use to create an optimized device for each patient.

Catheters from three different manufacturers spanning four commonly used Fr sizes were fully infused to determine the extent of changes from the infusion process. As apparent in Figure 3.1A, all tested catheters followed the same trend of the highest rates of oil infusion in the first 24 hours, followed by gradual increases and plateau starting at ~96 hours. Interestingly, there was consistency in the maximum degree of swelling of all the tested all-silicone catheters. The degrees of swelling for the brands were Bard 14 Fr: 56.51 (±0.75)%, Medline 16 Fr: 62.89 (±1.24)%, Bard 18 Fr: 59.96 (±1.2)%, and Dover 18 Fr: 55.01 (±3.18)%. The degree of swelling of the network is related to the degree of cross-linking within the network. Higher degrees of swelling would indicate less crosslinking; lower degrees would indicate higher crosslinking due to increased rigidity in the network.

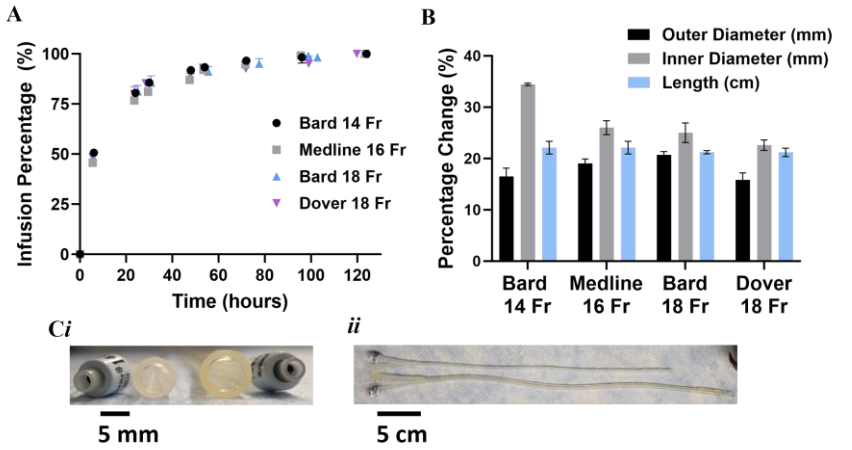

Figure 3.1. Comparison of the infusion of commercial all-silicone catheters and the resultant increases in important device parameters.

(A) Graph of the time dependent changes in mass of commercial catheter samples due to silicone oil infusion. (B) Graph of the corresponding changes in important catheter parameters due to infusion. (C*i*) Photograph of the cross-sectional view of untreated (left) and treated (right) Bard 14 Fr catheters. (C*ii*) Photograph of the length of untreated (top) and treated (bottom) Bard 14 Fr all-silicone catheters.

When comparing the parameter changes post-infusion, the inner diameter increased the most, consistent across all brands and sizes of silicone catheters. As seen in Figure 3.1B, the percent changes for inner

diameter were 34.44% for Bard 14 Fr, 26% for Medline 16 Fr, 25.01% for Bard 18 Fr, and a 22.61% increase in the Dover 18 Fr catheter. The changes in outer diameter were 19%, 16.51%, 20.69%, and 15.82%, respectively. This resulted in the fully infused 14 Fr Bard catheter changing to ~16 Fr, the fully infused Medline 16 Fr into a ~19 Fr catheter, and the Bard 18 Fr catheter to a ~22 Fr catheter. Photographs of the changes in outer diameter can be seen in Figure 3.1C*i*. The length was the parameter that changed most consistently across each tested catheter type: Bard 14 (20.12%), Medline 16 (22.11%), Bard 18 (21.24%), and Dover 18 (21.21%). The length of all measured silicone catheters increased from roughly 45 cm to about 54 cm (Figure 3.1C*ii*).

An observable trend can be seen when comparing these changes from unmodified of one size to fully infused from another. For example, infusion of the Medline 16 Fr catheter changed the inner diameter from ~3.19 mm to ~4.02 mm and the outer diameter from ~5.27 mm to ~6.26 mm (15.97 to 18.96 Fr). When comparing this to an unmodified Bard 18 Fr catheter, with an inner and outer diameter of ~3.46 mm and ~5.95 mm, respectively, the treated catheter provides a larger inner diameter for drainage compared to the 18 Fr while only slightly increasing the outer diameter. Furthermore, these results estimate how the starting materials change once infused, allowing for enhanced control in the treatment process to achieve a desired Fr size. Although catheters longer in length are reported to have longer drainage times when compared to ones shorter in length,[13] it is possible that the larger inner diameter could counteract any reductions in drainage time due to catheter elongation. These results show that the liquid treatment can be successfully applied to commercially available silicone catheters through the infusion of silicone oil, regardless of the brand.

3.2.2 Silicone Oil Overlayer Visualization

Adding a silicone oil overlayer onto the surfaces of commercially available catheters could enhance patient comfort and improve the antifouling performance compared to a standard silicone surface. This would be accomplished through the presence of oil, providing smoother insertion and increasing patient comfort by reducing stiffness in the material. The oil overlayer could act as a lubricant to reduce friction between the

catheter and host tissue, as claimed by CompactCath. However, with fully infused indwelling catheters, the question of how much oil is on the surface and how safe it is for continued use remains unanswered. Andersen and others (2018) demonstrated that low-viscosity silicone oil on the surfaces of liquid-infused catheters did not enhance inflammation in the bladder tissue of catheterized mice and was very effective at reducing the amount of Fg and pathogenic adherence to catheters.[45] Due to potential concerns existing with the use of high-viscosity silicone oil used in syringe coatings and surgical applications and the associated health risks,[76–78] further quantification of the amount of oil that has the potential to be lost into host tissue through mechanical removal from contact with the host tissue is needed. It will be valuable information for transitioning the use of this technology towards human use through clinical trials and the FDA approval process.

One method to detect silicone oil presence is to fluorescently label the silicone oil with one fluorophore while using a second fluorophore to label the bulk material. This enables the distinction between the two materials through confocal microscopy by taking successive images in the axial direction, allowing for quantification of the oil height.[62,86] As both materials needed respective dyes to visualize the interface, dyed materials were prepared as described in section 3.1.4.1. The degree of swelling for fully infused PDMS samples was 51.97 (±1.37)%, indicating similar crosslinking ratios as the commercial catheters as both materials were generally 2.0–2.5 mm thick. This was further confirmed by the ~96 hours it took for samples to become fully saturated with oil, which was very close to the commercial catheter samples. Due to the chemical similarity between silicone oil and PDMS, limited potential dyes worked for the system, and their respective excitation and emission spectra are very similar.

As seen in Figure 3.2, partially infused samples did not generate an observable liquid overlayer and were only seen in the fully infused and fully infused blotted samples (100 and 100B, respectively). This was consistent with the total infusion of silicone with silicone oil reported in the literature.[62,64,65] This can be explained by the strong swelling pressure that retains the silicone oil within the network due to the energetically favorable interaction between the two materials, leading to no formation of an overlayer.[86,87]

At 100% infused, the average oil overlayer height of 56.51 µm is similar to those found by Fong (2023), where the oil overlayer height of fully infused silicone materials was ~60 µm,[62] and by Kovalenko *et al.* (2018), who found oil overlayer heights ranging from 15–35 µm.[65] In the fully infused samples measured in this work, the average oil heights at the center of each sample were 66.64 (±4.67) µm, 31.76 (±2.62) µm, and 71.14 (±1.42) µm, resulting in large standard deviations. This could be due to the potentially uneven pooling of oil in the center of the sample where the measurements were taken due to the slight upward concavity of the samples. This was confirmed by analyzing the oil overlayer height at four corners of the samples. The average oil layer heights across all three samples for the top left were 23.25 (±10.72) µm, 30.74 (±19.34) µm for the top right, 17.49 (±2.88) µm for the bottom left, and 24.5 (±6.04) µm for the bottom right, displaying the unequal distribution of the oil overlayer height across the sample locations. The edges of the sample were avoided to reduce any edge effects that could influence results.

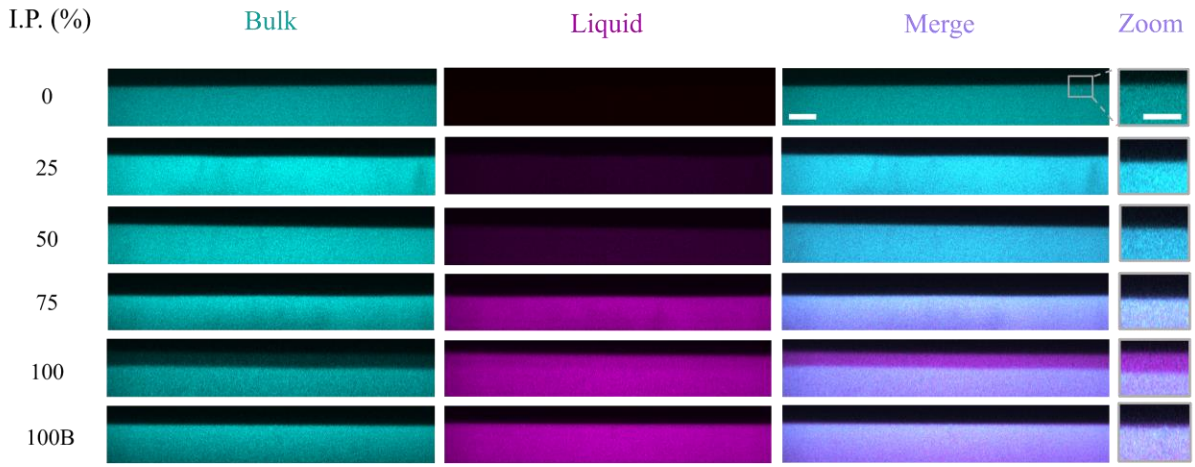

Figure 3.2. Confocal microscopy images of infused PDMS squares at varying percent infusions.

Cross-sectional confocal microscope images of the center of PDMS squares with different infusion percentages (I.P.%). The bulk channel corresponds to the polymeric matrix, while the liquid channel is the silicone oil. After imaging, the two channels were overlayed (merge channel). Images in the zoom channel are 200% zoomed in on the interface of each merged image for better visualization. False coloring was used. Scale bars 100 µm.

Once blotted with a cellulosic wipe, the oil overlayer height was reduced; however, large variations across samples were still present. The average overlayer heights at the center of the squares were 8.64 (±2.12) µm, 23.12 (±4.64) µm, and 7.24 (±1.38) µm, with the minimum and maximum measured heights being 5 µm–29.3 µm, respectively. The variation could be caused by uneven removal of the oil on the surface of the samples, resulting in oil splotches on the surface, which has been observed in other work.[66] This likely influenced the results seen, as evidenced by the oil splotches (dark spots) in Figure 3.3. However, there are inconsistencies when comparing the liquid layer heights post-blotting to those published in the literature. Post-blotting oil overlayer heights obtained by Fong (2023) were 500 nanometers (nm)—the axial resolution limit of a confocal microscope—in samples prepared with the fabrication and blotting procedures in this work before imaging.[62] The discrepancies in the results could be explained by more force being applied during the mechanical stripping process, which could have removed more or all oil from the surface through absorption.

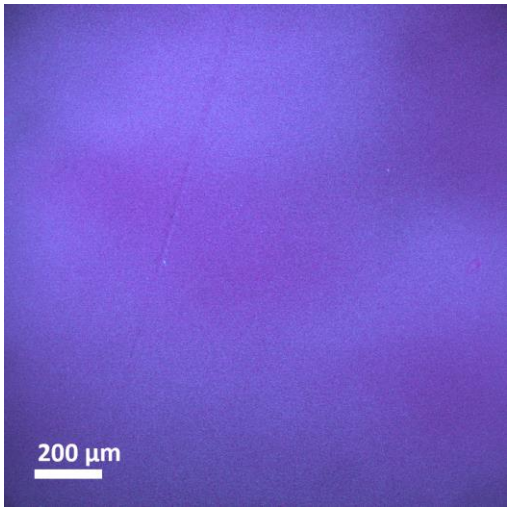

Figure 3.3. Oil pools on the PDMS surface after blotting.

An XY image of a fully infused and blotted PDMS sample surface taken with confocal microscopy. The dark spots represent small pools of oil present on the surface after blotting.

Using methods described in section 3.1.3.3, the lowest and highest recorded oil overlayer heights of unblotted and blotted samples were used to calculate the estimated oil mass that would coat the shaft surface of a 14 Fr catheter if the layer were uniform. Using the experimentally obtained values for the outer diameter (5.39 mm) and the shaft length (4.42 cm) of a fully infused 14 Fr all-silicone catheter allows for estimation of the amount of oil coating the surface. For the unblotted samples, the lowest measured height was 14.16 µm (the top right spot of sample 3), while the highest was 71.14 µm (the center of sample 3), resulting in a range between ~101 mg and ~512.5 mg of silicone oil. Due to the variation in the blotted

samples, the estimated mass of 20 cSt silicone oil coating the surface was not calculated, as no uniform layer was observed. However, as the Fr size of the catheter increases, more oil is expected to coat the surface correspondingly.

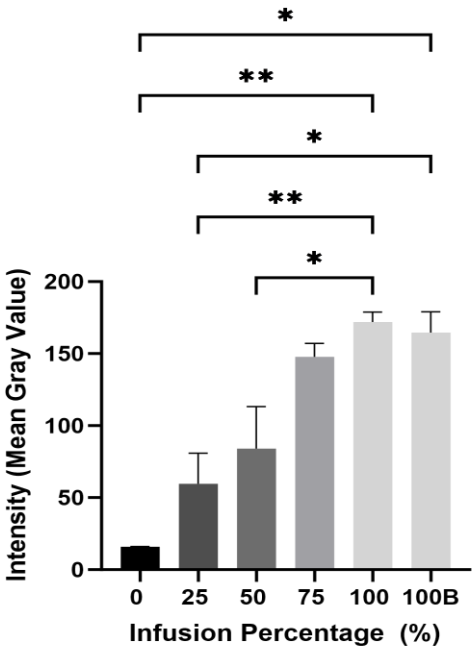

Figure 3.4. Mean gray value of the cross-sectional confocal liquid channel images per infusion condition.

The error bars are the standard deviation. Statistical significance between testing conditions was assessed using Kruskal-Wallis ANOVA. * = $p<0.05$ and ** = $p<0.01$. All comparisons are nonsignificant unless otherwise noted.

To better understand the changes in oil concentration at different percent infusion values, an intensity analysis of the cross-sectional confocal images was performed. The analysis was conducted following the protocol outlined in section 3.1.3.4. A general increasing trend in the intensity, as measured by the mean gray value (MGV), was found as the infusion percentage increased (Figure 3.4). Compared to controls, there were significant increases in the intensity of the 100% and 100% blotted samples ($p=0.0016$ and $p=0.0106$, respectively). When comparing partially infused samples, 25% and 50% were significantly lower than 100% infused ($p=0.0025$ and $p=0.0349$, respectively). The large increases seen in the mean gray value from 0 to 25% (61.1 MGV) and between 50% and 75% infused (51.13 MGV) and the variation in the 25 and 50% infused conditions are most noticeable. While it is much harder to tell the difference visually between 0 and 25% (Figure 3.2), the stark difference in color intensity for the 50 and 75% liquid channel images and the change from blue to purple in the merged images can be seen much more easily. The variation within the

lower partially infused samples could hint at differing oil distribution levels within the matrix in these conditions compared to the higher infusion percentages.

It is possible that intermittent urine flow on the inner surfaces of the catheter and extended contact with host urethral and bladder tissue on the external surfaces could remove any excess oil from the catheter[10]. Existing solutions from the literature provide helpful solutions to mitigate the amount of oil on the surface to levels that fall closer to the permitted daily exposure, which could prove beneficial in the context of liquid-infused catheters. One oil stripping method is exposure to an air/water interface. This method of enhanced oil removal removes excess oil from the surface due to the low surface energy silicone oil covering the high surface energy water at the oil/water interface, resulting in increased removal of the oil overlayer.[69,73] Lavielle and others (2021) used atomic force microscopy (AFM) to measure the oil overlayer height of PDMS samples fully infused with 10 cSt silicone oil after removal by exposure to flowing water to measure the regeneration over time.[63] It was observed that after 360 hours, the layer regenerated to one µm through oil migration from the bulk material to the surface. If the oil overlayer height coating a fully infused 14 Fr urinary catheter were one µm, the mass of silicone oil would be estimated to be ~7.28 mg.

Another emerging method for limiting the loss of free silicone oil liquid into the host environment is partial infusions of silicone catheters.[62] By only partially infusing silicone oil into silicone tubing, the liquid is far more likely to be retained within the bulk material due to swelling pressures and less likely to be expelled from the network and travel to the surface through syneresis.[86,87] Syneresis is a process where a liquid is expelled from the polymeric network and migrates to the surface.[63] Although no liquid overlayer would be present,[45] the effectiveness of partially infused materials has shown promising results in reducing the amount of Fg and pathogens that can bind to catheter surfaces.[62] Fong (2023) fabricated partially infused sections of the silicone tubing in groups of 10–30%, 30–50%, and 70–90% infused or fully infused and incubated the tubes with either Fg or *E. faecalis* to analyze the fluorescent signal through immunolabeling.[62] It was found that there were decreasing amounts of pathogenic adherence, indicated by fluorescent signal, as the infusion level increased. For Fg and *E. faecalis,* the first statistical difference in fluorescence

compared to non-infused controls was in the 70–90% group. Interestingly, no significant difference was observed between the 70–90% and fully infused materials.[62] Moreover, when measuring how much oil was lost from the surfaces of fully and partially infused materials through exposure to an air/water interface, fully infused samples lost significantly more silicone oil (~0.25 μL) compared to the 70–90% infused materials (~0.004 μL), which had no statistical difference in oil loss compared to non-infused controls.[62] This reduction in the partially infused catheters represents ~1.52 mg, demonstrating that partial infusions could be an effective alternative to fully infusing materials while achieving desired outcomes and limiting the amount of free liquid on the surface.

According to previous literature published by Hao *et al.* (2022), there exists a limited risk of adverse effects with inorganic silicon through oral ingestion, with an estimated permitted daily exposure (PDE) of 18,919 μg/day.[19] Alternatively, the PDE of silicone administered via inhalation or any other methods (i.e., subcutaneously, intraperitoneally, intravenously, intradermally, or intramuscularly) has a much lower PDE of 224 μg/day and 93 μg/day, respectively.[19] However, many studies used to derive these values were unpublished research by Dow Corning, a manufacturer of PDMS, where they delivered silicone oil to rats through repeated dosages of either 10 or 350 cSt silicone oil orally or by injections. For this reason, the accuracy of the limits remains unclear. Hao and others (2022) stated that these studies showed no toxicity responses and that the tested PDMS recovered unchanged in the feces.[19] The limited absorption of silicone oil in these studies could be explained by work done by Opperhuizen and others (1987), who found that silicone oils with an effective molecular length of greater than 43 angstroms (Å) did not pass through membranes such as the gastrointestinal tract in fish.[92] This equates to a number average molecular weight (MW) of 1050 (viscosity of ~10 cSt).[92] In the context of liquid-infused catheters, exposure to silicone oil via a liquid-infused catheter is not a repeated dose but is introduced entirely upon insertion. It is possible that free liquid on the surfaces of urethral or bladder tissue stripped from the surface due to urine flow or mechanical removal could be excreted from the body within the urine as it is released. Although 20 cSt

silicone oil was shown not to cause an increased immune response in bladder tissue after 24 hours *in vivo* when tested in mice,[45] further testing in humans is needed over a longer period.

3.2.3 Mechanical Testing of Infused Silicones

Both curing duration and temperature influence the mechanical properties of PDMS.[88,93–95] Infusing silicone oil into PDMS reduces mechanical strength as increasing amounts of oil are present in the matrix.[73,86] Softer materials could provide a smoother insertion process through lubricant and enhanced flexibility.[10,45] Still, if the material weakens too much, it could pose issues to the insertion process in a commercially treated catheter.[96] Therefore, it is paramount to quantify mechanical changes in the materials.

3.2.3.1 Tensile Testing

Tensile testing determines mechanical properties such as ultimate yield strength and Youngs's modulus of materials like metals, polymers, plastics, and composites. This property describes the rigidity of a given material and is calculated by dividing the tensile stress (force/area) by the tensile strain (change in length/initial length) in the linear region of the stress and strain.[14] This is accomplished by gripping the sample in the grip areas, applying increasing uniaxial tension stress to a test specimen, and slowly deforming the material until it fractures in the gauge region (Figure 3.5). Materials with lower elastic moduli are more elastic and can tolerate more deformation before failure. Typical ranges for the elastic modulus of PDMS fall within 1.32–2.97 MPa and are heavily dependent on both the cure temperature and the ratio of the base to the curing agent.[88,97] Curing temperatures are commonly anywhere from ~23 °C to 200 °C. Exceeding 200 °C has been shown to cause thermal decomposition of the material.[93] Dow Corning, the manufacturer of Sylgard 184 (one of the most commonly used PDMS elastomers[88]), recommends using a base-to-curing agent ratio of 10:1.[95] Still, ratios higher (e.g., 5:1) and lower (e.g., 20:1 or 30:1) are commonly found in the literature.[73,86–88,94]

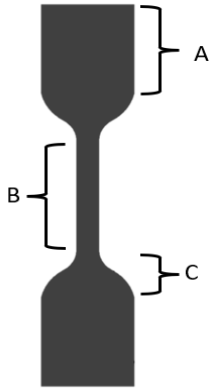

Figure 3.5. Schematic of an ASTM D412-C tensile specimen used in this work. (A) Grip area, (B) gauge region, and (C) reduced area.

Information on infused PDMS and the subsequent elastic moduli is limited, but Sotiri and colleagues (2018) tested the elastic moduli of 10:1 (base to curing agent) PDMS using nanoindentation to quantify how samples fully infused with 20 cSt silicone oil changed the mechanical properties of the bulk material. It was determined that pure PDMS cured at 70 °C had an elastic modulus of 2118 (±87.9) kPa, while the modulus of fully infused silicone (with 20 cSt silicone oil) was reduced to 1429 (±58.77) kPa with fully infused samples (Figure 3.6A).[73] This information is relevant for the extremes of the infusion process but offers little on the mechanical strength of partially infused silicone materials. Previously, it has been shown that increasing swelling ratios decrease a material's stiffness, but this was demonstrated with lower curing ratios.[86,87]

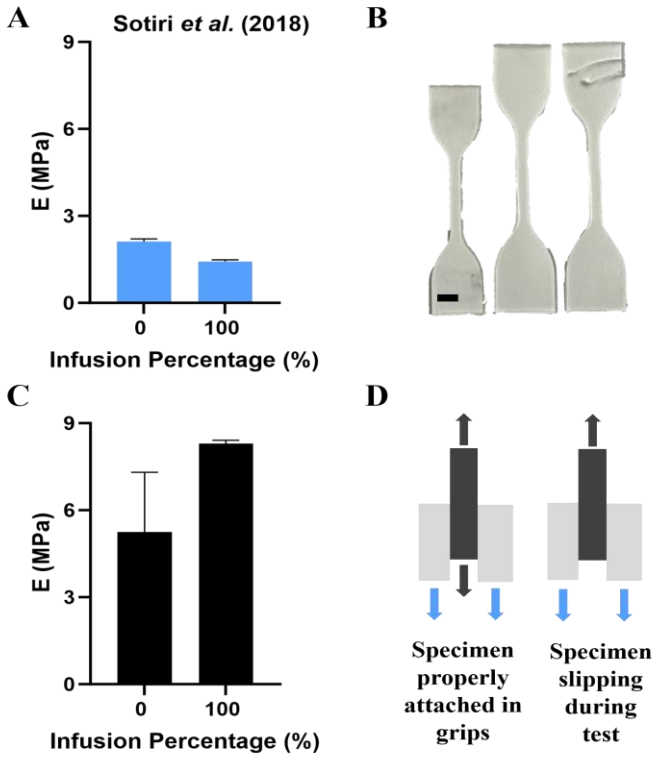

Figure 3.6. Tensile Testing of Infused Specimen Results.

(A) Elastic modulus data obtained by Sotiri *et al.* (2018) through nanoindentation. (B) Images of test specimens used to generate data in (C). Left to right: uninfused, fully infused, and fully infused specimen with laceration from overtightening of grips. (C) Measured elastic modulus collected as part of this study through tensile testing in this work. (D) Schematic of sample slippage during testing. The error bars in the graph presented represent the standard deviation. The scale bar is 10 mm.

To better understand the gross properties of infused PDMS, we fabricated specimens following the standardized American Society for Testing of Materials (ASTM) D412-16: Test Methods for Vulcanized Rubber and Thermoplastics-Tension type-C dimensions before infusion. However, it was found that the grip region of fully infused samples did not fit in the tensile testing grips during preliminary testing. This resulted in the width of the gauge regions being 20% too wide, causing

unequal force to be applied on the sample in contact with the grips compared to the area of the specimens outside of the grips region when the grips were tightened. Notable lacerations in the specimen formed, rendering the specimen defective before the test had begun (Figure 3.6B). The initial ASTM dimensions result in samples that are just smaller than the width of the grips and do not account for materials that increase in size due to the incorporation of a solvent. Therefore, a 3D printed mold with dimensions 75% of the initial values was fabricated to account for this once samples were infused.

Data for the elastic modulus collected during tensile testing was inconsistent with those previously reported for infused and non-infused materials. Control samples had an average elastic modulus of 5.25 (±2.06) MPa (Figure 3.6C), which is almost double the values reported by Sotiri *et al.*, and was closer to PDMS that had to cure temperatures closer to 200 °C or lower crosslinker to base ratios.[73,88,93,97] Up to 75% infused, the elastic modulus for controls shows a decreasing trend, showing that higher degrees of infusion result in lower elastic modulus values. Interestingly, once fully infused, the elastic modulus was higher than the data measured for control samples. Further, it was inconsistent with the findings by Sotiri and others (2018). The inconsistencies in the testing results are most likely due to the choice of grips and the lack of an extensometer while conducting testing. The results indicate that the testing methods must be improved to provide more accurate tensile testing data. Full tensile testing results can be seen in Appendix B.

MTS advantage wedge grips were the only type of grip on the load frame used for testing. The operator tightens these grips by hand, securing the samples to limit sample slippage. According to the MTS website, wedge grips are ideal for testing rigid materials, such as metals, ceramics, plastics, or composites. With the softer silicone oil-infused samples with varying heights, finding the balance in the applied force to the sample to prevent laceration of the grip region before testing but tight enough to limit specimen slippage during testing (Fig 3.6D) was difficult. Slipping of the samples would result in increasing crosshead displacement but limited increases in tension in the gauge region of the sample. The upper grip and load cell are attached to the crosshead, which moves vertically, applying tension to the sample. This is likely the cause of the high elastic modulus values reported. Grips designed explicitly for testing elastomeric

materials, such as pneumatic grips, which apply constant pressure throughout testing, are more optimized for tensile testing of thin films and elastomeric materials and would have aided in reducing sample slippage. In addition, having an extensometer, which measures the elongation of the gauge region of a tensile specimen throughout the testing process, would be beneficial. Without one, the machine software reports the load frame crosshead displacement as the total elongation of the sample. However, sample slippage could result in differences between the actual elongation of the gauge region and crosshead displacement. Despite their benefits, an extensometer was not chosen for this work because the naturally flexible silicone material could not support the extensometer during abrupt breaks once the sample broke. If an extensometer were to be present on the sample during this, it would likely fall off the sample and could break.

3.2.3.2 Shore Hardness Testing

Shore hardness testing quantifies the hardness of polymeric or plastic materials. Hardness can be measured using a Shore durometer, where an indenter tip is pressed into the sample, and the indentation depth is translated into a hardness value.[98] Shore hardness testing encompasses various scales, each of which is ideal for measuring certain types of polymers or plastics. For instance, the Shore A scale is commonly used to test the hardness of vulcanized rubbers, soft plastics, and silicones, while Shore OO, the scale below A, is used to test highly soft plastics, rubbers, and foams.[98] Each scale spans from 0 to 100, with higher values indicating a greater hardness and lower values indicating softer materials. The further the indenter penetrates a sample, the lower the hardness reading. As specified in ASTM D2240-15: Test Method for Rubber Property Durometer Hardness, hardness values below 20 and above 90 are not considered reliable.[98]

Durometers have been used to quantify the hardness of PDMS with varying curing agent ratios, curing durations, and temperatures in previously reported literature,[88,94,99] but limited data exist on how the infusion of silicone oil into PDMS impacts the hardness. A recent study conducted by Guerrero-Vaca and colleagues tested PDMS (10:1 base to curing agent, cured at 23 °C for 48 hours, then at 100 °C for one hour) incorporated with varying weight percentages of 100 cSt silicone oil to either 5, 20, or 50% percent oil for use as a release agent in polyurethane molding processes.[99] It was found that control samples had a Shore

A hardness of 43, in agreement with manufacturer specifications and literature,[88,95,100] and samples fabricated with 50% silicone oil had a Shore A hardness of 17.[99] Reductions in hardness could be due to the limitation or inhibition of the maximum number of crosslinks within the network, as the polymer chains want to maximize polymer-solvent interactions and can do so before curing solidifies the network.[73] Further, higher percentages of oil occupy more space, which could disperse polymer chains that are otherwise available to crosslink. Although these studies used fundamentally different sample preparation methods, they demonstrate that durometers can successfully record hardness changes due to the incorporation of silicone oil into PDMS.

To test the Shore Hardness of our infused PDMS samples, we fabricated them following the methods outlined in section 3.1.6. All silicone samples were fabricated to be ~6 mm tall per ASTM D2240-15. Samples that are not adequate in height result in inaccurate data with higher hardness values due to unintended measurement of the surface the sample is resting on into the value. Individual measurement points needed to be at least six mm apart and 12 mm from the edge. To reach complete infusion, it was observed that samples required about 35 days compared to the fabricated silicone squares or all-silicone catheters, which required ~6 days to achieve equivalent levels of infusion but followed similar trends with the highest increase in mass early in the infusion process. As seen in Figure 3.7, increasing the amount of silicone oil infused into the PDMS solid decreases the Shore hardness values of samples in both scales. This is consistent with previously published literature describing the reduction of the PDMS mechanical properties due to the incorporation of silicone oil.[73,99,101] Further, the obtained 46.6 (±0.91) Shore A hardness for control samples was very similar to the interpolated hardness value of 46.68 Shore A from reported data for control samples cured at 70 °C found by Johnston *et al.* (2014).[88]

After 25% infusion, the more sensitive Shore OO durometer provided better insights into the changes in hardness, evident by the plateau in Shore A hardness but a decrease with Shore OO while testing the same samples (Figure 3.7). Regardless of the scale used, there were substantial reductions in hardness as soon as 25% infusion compared to controls ($p=0.0007$). The limited change in Shore OO hardness between 25%

and 50% infused (83.08 ±0.76 and 82.92 ±0.49, respectively) could be due to an inadequate volume of oil present in the matrix to cause further significant changes. As seen in the confocal imaging data (Figures 3.2 and 3.4), there were similar intensities of the silicone oil channel of 25% and 50% infused samples (79.1 and 98.9, respectively). However, marked increases were seen from 0% to 25% (63.1 MGV) and from 50% to 75% infused condition (51.13 MGV), corresponding to statistically significant reductions in sample hardness. At 25%, there could be enough oil to decrease the overall hardness but not enough oil to cause substantial adjustments at 50%. However, once samples are 75% infused, enough oil may be present to reduce hardness significantly (p=0.0039). Although the change in intensity between 50 and 75% was insignificant, it still provides corroborating evidence for this trend. The hardness was only measured at five points for each of the five samples tested per infusion percentage, so further replication is needed to corroborate these findings.

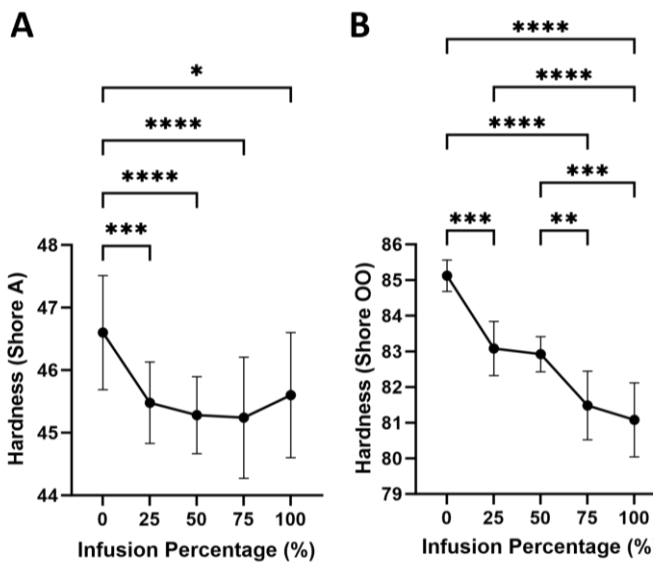

Figure 3.7. Shore hardness testing of liquid-infused PDMS. (A) Shore A and (B) Shore OO hardness of infused PDMS durometer samples. In all graphs presented, the error bars are the standard deviation. Statistical significance between testing conditions was assessed using Kruskal-Wallis ANOVA. * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, **** = $p<0.0001$. Unless otherwise stated, comparisons were nonsignificant.

When fully infused, no significant differences were observed in the hardness of PDMS samples compared to 75%. Most noticeably, in Shore A, the obtained hardness increased from 45.24 (±0.97) at 75% to 45.6 (±1) at full infusion. Regardless of the Shore scale used to measure the hardness of the infused samples, the 100% infused samples had significantly lower hardness measurements when compared to the control samples. With Shore OO, the hardness of all tested samples was considerably lower than that of controls

($p<0.0001$) compared to the reductions seen with Shore A ($p=0.0137$). Although more noticeable in results obtained with the Shore A scale, there was evident variation in the hardness of samples throughout this experiment. The large standard deviations in hardness could be attributed to slight differences across each sample but also a result of the limitation of precision with the instrument itself. These devices had dial gauges that ranged from 0–100, with one-unit increments and a needle to indicate the measured sample hardness. Therefore, measurements were rounded down if the needle was between two numbers, contributing to increased variation. The use of a digital durometer would likely reduce the extent of variation due to increased precision with each measurement. Overall, changes in the hardness of the bulk material are within about two Shore A and near five Shore OO, showing minor changes due to infusion.

3.3 Summary

Confocal imaging confirmed the generation of an oil overlayer from infusion, agreeing with previously published results of fully infusing PDMS with silicone oil. Further, the 56.51 μm average liquid layer height was reduced through mechanical removal. After blotting, the obtained liquid layer was found to be highly variable, but it could have been due to small pools of oil on the sample surface, as observed previously[66]. Through Shore hardness testing, it was found that the material's hardness was reduced at varying infusion levels through the elongation of the polymeric chains as the oil occupied more space within the matrix. Similar reductions in the elastic modulus of fully infused samples were found by Sotiri *et al.* (2018), corroborating the trend seen.[73] However, in partially infused samples, there could be differences in the oil distribution in the matrix, suggested by the intensity of the oil channel from confocal imaging. Lower infused conditions (25% and 50%) showed the most variability of any infusion percentage measured, hinting that partially infused samples may require more time for the oil to equilibrate within the sample. These results provide insights into what is occurring within the PDMS and at the interface, but changes in catheter functionality must also be determined.

Chapter 4

FUNCTIONALITY TESTING OF LIQUID-INFUSED SILICONES

The changes caused by the infusion of silicone oil into commercially manufactured catheters have been quantified thus far, but the functionality of the devices after treatment has yet to be determined. Functionality testing for a urinary catheter would include ensuring the proper functionality of all device components—such as the balloon and the inflation valve—through benchtop testing in conditions that simulate the intended use environment. Preclinical performance data are essential for aiding the transition of a medical device from benchtop to use in humans. This chapter investigates the performance and functionality of fully infused commercially available all-silicone urinary catheters through benchtop functionality testing of individual catheter components, sterilization, and ASTM F623-19: Standard Performance Specification for Foley Catheter-compliant testing. By completing custom and standardized preclinical functionality testing, we can better understand the performance of liquid-infused catheters.

4.1 Materials and Methods

4.1.1 Benchtop Functionality and Performance Testing

4.1.1.1 Syringe Port Valve Testing

To test if the infusion of the inflation valve—or syringe port—was limiting its functionality through increased resistance during the inflation/deflation of the balloon, Bard 14 Fr all-silicone catheters were submerged in 20 cSt silicone oil from the middle of the shaft region and below. To ensure equal infusion through the presence of silicone oil in the inner lumen, five mL syringes (Luer-Lock, BD) were placed into the drainage lumen and used to create a vacuum and hold silicone oil in the inner catheter lumen equal to the point where the external surface of the catheters was submerged. Catheters were submerged for six days to ensure full infusion of the lower shaft region. Catheters were removed, and the excess oil was allowed to drain, followed by mechanical wiping of the exterior surfaces with a cellulosic wipe. To test balloon functionality post-infusion, 10 mL of DI water was injected into the syringe port, filling the five cubic centimeters (cm^3) balloons. The test's success was qualitatively determined by the relative effort needed to

inflate and deflate the balloons compared to catheters with balloon inflation valve regions fully infused with silicone oil.

4.1.1.2 Dimensional Shrinkage Test at 37 °C Over Standard Use Cycle

The shafts of 12 Bard 14 Fr all-silicone catheters were fully infused with 20 cSt silicone oil for six days. Subsequently, the catheters were removed, and excess oil was allowed to drain before blotting with a cellulosic wipe. Each catheter shaft's mass, inner and outer diameter, and length were recorded before being placed in an incubator (MaxQ 6000, Thermo Scientific) at 37 °C for one, two, three, or four weeks. Three catheters were removed at each interval, and parameters were measured. Additionally, three fully infused controls were monitored at room temperature (23 °C) to act as controls for the temperature, and three non-infused catheters were placed in the incubator as controls for the infusion of silicone oil over the four-week testing cycle.

4.1.1.3 Steam Sterilization

Excess silicone oil was removed from fully infused urinary catheters as described in section 4.1.1.2. Catheters were folded into a U-shape and placed in individual 12-inch (in) x 6-inch Self Seal Tyvek™ Steam Sterilization Pouches (Keystone Cleanroom Products). The pouches were placed in an autoclave (2540M, Tuttnauer) at 121 °C and 26 pounds per square inch (psi) for 60 minutes. The pouches self-sealed during autoclaving and were examined to ensure the process indicator had changed color to ensure proper sterilization of materials before use.

4.1.1.4 Droplet Speed Testing

Fully infused catheters were autoclaved as previously described and removed from their packaging. two cm sections were cut out of the shaft region using a razor blade and placed on a tilt stage (AP180, Thorlabs) set to 30°, which was verified using a digital angle gauge (AccuMASTER 2 in 1 Magnetic Digital Level and Angle Finder, Calculated Industries). A 20 microliter (µL) droplet of crystal violet (CV) dye (Harleco) was pipetted into the inner lumen of the tubing, and a smartphone camera was used to record the time for

the droplet to slide to the bottom of the tube. Droplets that remained stationary after being deposited in the lumen were marked as stuck and assigned values of 30 seconds.

4.1.2 Modified ASTM F623-19 Functionality and Performance Testing

ASTM F623-19 was used for functionality and performance testing of infused all-silicone catheters. All test samples were Bard 14 Fr all-silicone Foley catheters infused with 20 cSt silicone oil, which had excess oil removed from the inner lumen and outer surface, as previously outlined. Catheters were then inflated with 16 mL of DI water and subjected to the respective testing procedures and conditions. The respective lot numbers for materials used in testing can be found in Table C.1.

4.1.2.1 Balloon Size and Shaft Size

A 3D-printed Fr size gauge was printed out of polylactic acid (PLA) filament, adhering to the outlined Fr size chart specified in section 3.12 and the tolerances in Annex 5.4.1 of ASTM F623-19 (2019). The same printer and methods were used to prepare the desired object, as described in section 3.1.4. Polylactic acid (PLA) filament (Overture) was used to print desired objects using a nozzle temperature of 215 °C and a build plate temperature of 60 °C. The layer height was 0.2 mm, and the infill was set to 15% in a gyroid pattern.

4.1.2.2 Inflated Balloon Response to Pullout

A borosilicate glass funnel (ULAB) with an internal shaft diameter of about nine mm was suspended in a ring stand (positioned at the table's edge) at the V-shaped region, mimicking the urethra and bladder outlet. For each test, the proximal end of the catheter was fed through the inner lumen of the funnel, where the balloon was inflated with 16 mL of DI water and allowed to rest on the inner surface of the V-shaped region of the funnel. A 454 g (one pound) weight was attached just above the Y splitter region of the catheter before testing. two tests were performed: 1) a two-minute static load test where the load was suspended from the end of the catheter, and 2) an impact load test where the weight attached to the catheter was lifted 0.6 meters (m) above the natural static hanging point and subsequently dropped. Test failures were indicated by either

balloon rupture or passage of the entire balloon (and, therefore, the whole catheter) through the barrel of the funnel.

4.1.2.3 Resistance to Rupture

Fully infused catheter balloons were inflated the balloons with 16 mL of DI water using a 10 mL syringe (Luer-lock, BD). Following, they were placed into a 1000 mL Pyrex glass beaker containing 750 mL of artificial urine with a pH of 5.5–7. The recipe for artificial urine is described in Table X.3: Composition of Artificial Urine of ASTM F623-19 (2019), and the pH was adjusted into the appropriate range. The beaker containing the catheters and artificial urine was covered with tinfoil and incubated at 37.8 °C for seven days. Any catheters with burst balloons failed the test, and deflated balloons resulted in an invalid result.

4.1.2.4 Deflation Reliability

Test sample balloons were inflated through the inflation syringe port with DI water, submerged in a two-liter high-density polyethylene (HDPE) container of DI water, and placed into an incubator at 37.8 °C for seven days. The container was covered to prevent evaporation throughout testing. After seven days, catheters were removed from the DI water and drained by connecting a 10 mL syringe to the syringe port inflation valve or by cutting the catheter approximately 13 mm distal to the balloon if no drainage occurred into the syringe. Balloons were given 15 minutes to drain and had to be no greater than four Fr sizes (~1.32 mm) larger than the label Fr size to pass the test. Failures were determined by the inability to deflate or balloon greater than four Fr sizes larger than the label size after the draining period.

4.1.2.5 Balloon Volume Maintenance

The balloons of fully infused catheters were inflated with a 0.5 mg/mL solution of methylene blue (LC169407, LabChem) in DI water and placed on a cellulosic wipe to act as a visual indicator of leakage from the balloon. Test samples were covered with tinfoil to protect them from light throughout the 24-hour test duration. Failures were classified as discoloration of the indicator surface caused by dye leakage.

4.1.2.6 Statistical Analysis

Statistical analysis of data was conducted using GraphPad Prism, Version 10 (GraphPad Software). The statistical significance of the experiments was tested using a Kruskal-Wallis one-way analysis of variance (ANOVA) tests. Significance values are: *= $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, **** = $p<0.0001$.

4.2 Results and Discussion

4.2.1 Benchtop Functionality Testing

4.2.1.1 Sectional Infusion and Syringe Port Valve Functionality Test

When catheters were fully submerged in the infusion process, the function of the valve contained within the syringe port that regulates the volume of the balloon was hindered. It required a significant amount of force to achieve suboptimal function compared to the relative ease of operation of the inflation valve of an unmodified commercial catheter (Figure 4.1). As these devices have been designed and tested to adhere to specific performance standards, manipulating certain parameters can cause issues. As the valve materials themselves are unaffected by infusion as they are commonly made of either polypropylene (PP) or polyvinyl chloride (PVC)[17], it was hypothesized that the expansion of silicone material surrounding the valve was limiting valve function. Only the shaft region of the catheter proximal to the Y-splitter is directly inserted into the patient, so the infusion of the shaft was conducted to determine how sectional infusion of the catheter would influence functionality.

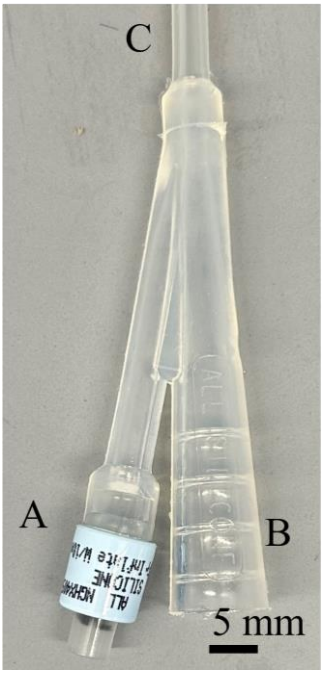

Figure 4.1. Y-splitter region of a Foley catheter.

An image of the (A) inflation valve, (B) drainage port, and (C) the shaft of an all-silicone Foley catheter.

As hypothesized, sectionally infusing the catheters resulted in valve functionality similar to unmodified controls. Both inflation and deflation were completed multiple times per test sample with relative ease, resulting in this being the recommended infusion method if this

technology was scaled up. With this infusion method, there will be no antifouling coating on the inner and external surfaces of the syringe inflation or drainage ports. Theoretically, the liquid layer coating the shaft would likely reduce bacterial and microbial colonization more effectively than unmodified controls. Furthermore, regarding patient comfortability, the lack of infusion of this region may allow for better concealment of the catheter. These parts of the catheter may typically be placed under clothing, and silicone oil could easily be absorbed into garments worn by the user. Critically, it has been shown that the coating can be applied while preserving the functionality of the syringe inflation valve.

4.2.1.2 Parameter Shrinkage at 37°C Over Standard Use Cycle

PDMS has a standard operating range between -45–200 °C.[93,95] While body temperature (~37 °C) is well within this temperature range, the reduction in the mechanical properties of the material due to infusion with silicone oil could influence measured parameters of the system over the standard use cycle of ~28–30 days.[73,86,87] Namely, issues resulting from this would be a restriction of the inner diameter, limiting the drainage rate of urine, or a change to the outer diameter. These concerns could increase patient discomfort and functionality of the device if they occur. To test for potential changes in essential parameters over the standard use cycle, test samples were prepared and tested as described in section 4.1.1.2.

The mass of fully infused catheters at 37 °C was slightly reduced throughout the testing period, evidenced by the overall percent change ranging from 0.5–1% and ending at 0.65% (Figure 4.2). Fully infused catheters at room temperature (23 °C) showed a slight decrease in mass during the experiment, while the unmodified samples remained very close to 0. The change in mass could cause a slight restructuring of the silicone matrix, which is evident in the other parameters. Data collected for the inner diameter shows variability in the inner diameter over time but results in an overall increasing trend. In this subset of parameters, the most deviation between measurements is evident in this parameter. Three test samples per condition were measured per week. For week 1, the percentage changes were -0.29%, -1.73%, and -3.7%, while for week 4, the percentage changes were 2.76%, 0.29%, and -0.60%. The actual trend is likely that there is a slight increase or no increase, similar to the control samples, but the data from weeks 1 and 4

likely exaggerate this effect. This explains the observed deviations in inner diameter compared to controls, which both increased slightly. Outer diameter increased slightly over time—0.8% by week 4—while both control conditions had percent decreases in parameter size. This was the only parameter that did not mirror the general trends in control samples. However, this minor increase in size from 16.33 Fr to 16.45 Fr would likely not cause additional harm to the patient throughout the use cycle and is well within the ±1 Fr size tolerance for the shaft of all-silicone catheters, as stated in the Foley catheter-specific standardized testing documentation.[102] The length of the catheter shafts decreased slightly until after week 1, when the average change in length plateaued for the duration of testing. The decrease in length could contribute to the increases observed in inner and outer diameter, as the mass only changed slightly. All parameters aside from inner diameter had less than a 1% increase or decrease after four weeks. Even if the percent increase in inner diameter was accurate for week 4 when tested with larger sample sizes, it is a 1.22% increase from initial measurements. These results suggest that the limited dimensional changes in the measured parameters highlight that the catheters would retain their structure after liquid infusion throughout the standard use cycle and would likely not influence performance.

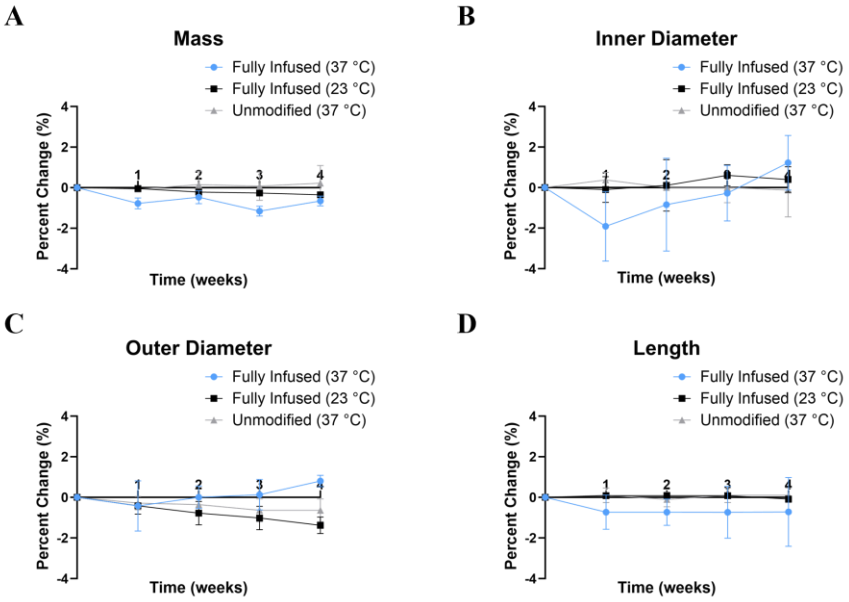

Figure 4.2. Percent change in parameters of fully infused or unmodified all-silicone catheters subjected to different temperatures over a four-week standard use cycle. (A) Mass, (B) inner diameter, (C) outer diameter, and (D) length. In all graphs presented, the error bars represent the standard deviation.

4.2.1.3 Sterilization of Liquid-Infused Catheters and Sliding Droplet Test

Silicone tubing is an essential component in various medical devices ranging from catheters to endoscopes, dialysis tubing, and tubing used for pharmacological applications, necessitating vast quantities of silicone material to be sterilized daily before packaging and eventual use.[18] Sterilization of single-use medical materials, especially invasive ones such as catheters, is essential to retain sterility and patient safety. The most prevalent medical product sterilization methods are electron-beam (e-beam), ionizing radiation, ethylene oxide (EtO), and steam sterilization,[17] with each method better suited to different material attributes and manufacturing processes. Although EtO is commonly used to sterilize catheters, steam sterilization was used due to availability and cost.

Previously published studies have found lubricant-infused surfaces to be effective antifouling surfaces due to the low contact angle required for making water droplets slide off and high droplet sliding rates.[62,66,67] However, this has yet to be tested using commercially manufactured catheters and, more importantly, if antifouling functionality is retained following sterilization. This is essential because medical devices must be sterile before patient use to prevent the introduction of pathogens from contaminated materials to the urinary system.

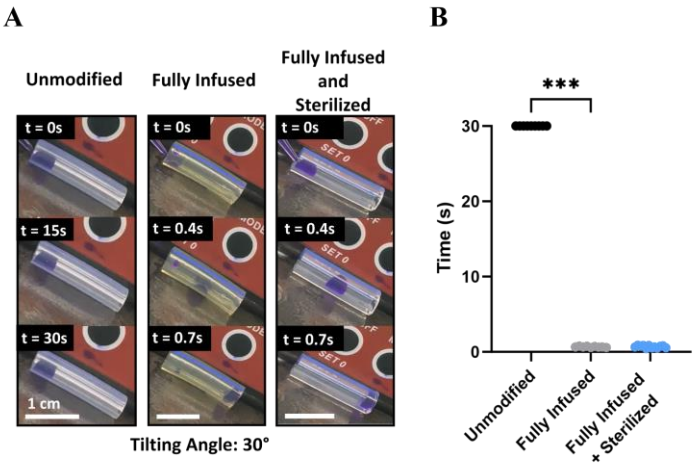

Figure 4.3. Catheter droplet sliding time pre- and post-sterilization.

(A) Images of CV droplet sliding time testing on fully infused sections of catheters infused with 20 cSt silicone oil pre- or post-sterilization through autoclaving. (B) Results from droplet sliding test. In all graphs presented, the error bars are the standard deviation. Statistical significance between testing conditions was assessed using Kruskal-Wallis ANOVA, *** = $p<0.001$. Unless otherwise stated, comparisons were insignificant. Scale bar 1 cm.

As seen in Figure 4.3, the crystal violet (CV) droplets remained stationary on the inner lumen of unmodified

catheters and never made noticeable progress toward the end of the tube in all experimental runs. In contrast, the fully infused materials showed a significant reduction ($p=0.0002$) in the average time it took the droplet to reach the end of the tubing (0.66 seconds) compared to the unmodified catheters (>30 seconds). Furthermore, once fully infused catheters were autoclaved and subsequently tested, the droplets took 0.69 seconds to reach the bottom, statistically different from controls ($p=0.0007$). Notably, there was no statistical difference in sliding times ($p>0.9999$) between the two test conditions, demonstrating sustained antifouling ability. The compatibility with other commonly used sterilization methods, such as EtO, remains to be answered.

4.2.2 Modified ASTM F623-19 Testing of Liquid-Infused Catheters

With standardized testing, it becomes easier to compare the performances of one product to another, as testing methods and materials may not be consistent across each testing facility. Independent regulatory bodies such as the American Society of Testing and Materials (ASTM) or the International Organization for Standardization (ISO) are international organizations that publish documentation outlining standardized manufacturing and testing guidelines and procedures that allow for reproducible data collection. ASTM F623-19: Performance Specifications for Foley Catheters outlines a comprehensive series of tests and thresholds that a given Foley urinary catheter must pass to be considered safe and effective for patient use and standardizes the data collection to allow comparison across testing facilities. These tests are designed to act as benchmarks for proper functionality and allow for gauging performance compared to commercially available catheters when exposed to test conditions meant to mimic the intended use environment. Ensuring the Foley catheter balloon's adequate function is imperative to facilitate correct placement and urine drainage throughout use. As seen previously, the addition of silicone oil into the system resulted in changes in mechanical properties and important parameters and thus required testing to ensure that it does not hinder the intended functionality of the urinary catheter or any of its components. It was noted in preliminary testing that the expansion of silicone material in the balloon region resulted in balloons that required about ~16 mL of water to inflate to be comparable in shape to that of the control catheter balloons. For this reason,

all modified ASTM F623-19 testing with liquid-infused all-silicone catheters was conducted where balloons were inflated past the recommended 10 mL that unmodified catheters are tested at. Further, as only infusing the shaft region of the catheter demonstrated no reduction in balloon inflation port functionality, all catheters subjected to ASTM F623-19 testing were sectionally infused to facilitate proper inflation and deflation of samples.

4.2.2.1 Flowrate Through Drainage Lumen

This test is designed to test the drainage rates of 14–26 Fr catheters, with a minimum passing threshold of 100 cm^3/minute. As the infusion of silicone oil causes the inner diameter of the catheter to increase on average ~27%, this change would increase the drainage rates relative to unmodified catheters. As the tested Bard 14 Fr all-silicone catheters are already designed to provide passing results for this test, the drainage rate of fully infused materials would likely exceed the threshold of 100 cm^3/min. For this reason, this specific test was not conducted.

4.2.2.2 Balloon and Shaft Size

This test was not conducted as the external surface is being modified. The determination of whether the treated materials adhered to the allowed tolerances was completed after testing. Information on the ability of samples to adhere to allowable tolerances after respective testing can be found in section 4.1.2.1.

4.2.2.3 Inflated Balloon Response to Pullout

The balloon anchors the indwelling catheter within the patient's bladder and must be strong enough to resist sudden pullout forces or suspended weights, such as a urine collection bag. If the balloon ruptures due to a sudden tension force on the part of the catheter outside of the body, balloon fragments can remain in the bladder, which can cause irritation, chronic infection, or catheter blockages.[103] Further, as observed in preliminary testing, infusion of the balloon region of the catheter required inflating the balloon with higher volumes to achieve a similar shape (Figure 4.4A). Therefore, it is imperative to understand whether the

silicone balloons of liquid-infused silicone catheters retain proper levels of balloon integrity during static and impact testing with a standardized load.

To test this, a one-pound (~454 g) load was affixed just proximal to the region where the catheter shaft meets the drainage and syringe port tubing, and static and impact load testing was conducted by replicating a testing setup per ASTM F623-19 guidelines, as seen in Figure 4.4B and 4.4C. All three balloons inflated with 16 mL passed the static load test, but one of the balloons ruptured when subjected to the impact load test. Importantly, it was noted that the balloon survived the initial impact but ruptured during the rebound. Volumes of 14 and 18 mL were also tested, with all 14 mL surviving the static load tests and two out of three surviving the impact load test. Out of three 18 mL inflated test samples, one failed the static load test, and one out of two surviving balloons failed the impact test. This could be explained by the increased stress on the balloons due to suboptimal inflation volumes coupled with the presence of the lubricant layer. Although all samples were blotted, the thin layer of lubricant, as observed in the confocal imaging, could cause increased balloon slippage. Regardless of the inflation volume, it was noted that there was variability in balloon shapes, which likely

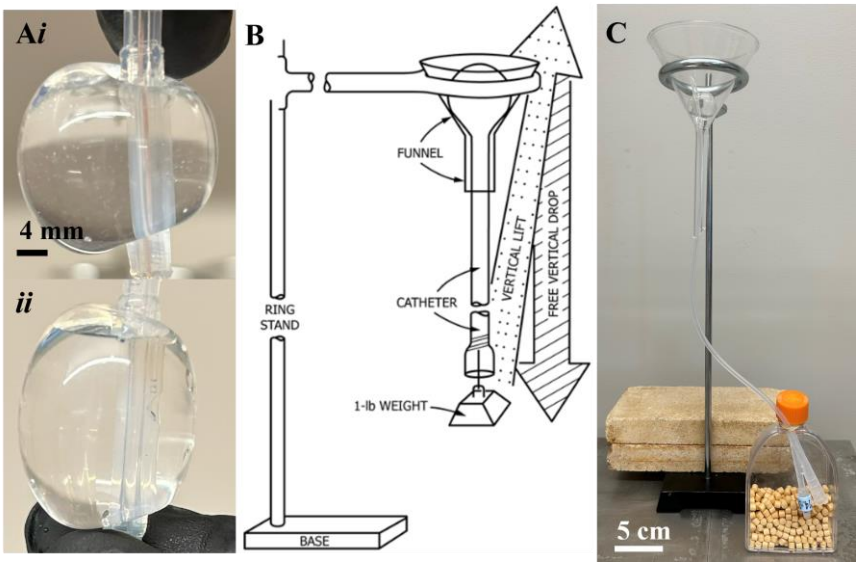

Figure 4.4. Inflated all-silicone balloon shapes differences and the resistance to pullout testing setup.

Images of the balloons of (A*i*) an unmodified catheter inflated with 10 mL of water, and (A*ii*) the balloon of a fully unfused catheter inflated with 16 mL of water. (B) Schematic of static and impact load testing setup, as found in ASTM F623-19, and (C) an image of the testing setup used in compliance with the ASTM guidelines.

contributed to the results seen. As the catheters were submerged in a dish of silicone oil, the bottom section of the balloon was likely in contact with the dish, which could have slightly altered infusion in this area compared to the rest. This could cause discrepancies in the shape of the balloons once fully infused and inflated. Suspending them in a vat where the entire section of the balloon is in contact with the oil may provide better results once inflated.

4.2.2.4 Resistance to Rupture

Samples were prepared, and testing was conducted as outlined in section 4.1.2.3. Before submersion, the pH was adjusted to 5.8 to fall within the accepted range. During preparation for the test, it was noted that test sample three had non-uniform balloon inflation, with one side of the balloon more inflated than the other. Out of four tested samples, only one passed with an intact balloon after seven days. Interestingly, it was observed that the three failures occurred within the first two hours of testing. This could be due to point defects in the balloons with failures or from handling the devices when removing excess oil before testing. The weakening of the balloon material due to the infusion and increased inflation volume could allow for the chemicals present within the artificial urine to cause the balloon material to degrade and eventually rupture. Further testing using the same fabrication methods is needed, but altering the infusion method could reduce observed discrepancies in balloon shape and size, as discussed in section 4.2.2.3.

4.2.2.5 Deflation Reliability

Foley urinary catheter balloons must reliably deflate as desired for removal in case of an infection or if a change of materials is necessary. When an unmodified catheter is removed from its packaging and subsequently inserted into a patient, the balloon is flush against the shaft and inflates when liquid is injected into the syringe port valve to secure the device in place within the bladder. As outlined in the ASTM documentation, the balloon has an acceptable plus four Fr size tolerance when first removed from the packaging and deflated after use. During the removal process, the water is first removed from the balloon before the entire catheter is withdrawn.[104] To ensure consistency in size before and after use, the treated shafts and balloons of four all-silicone catheters were measured after removal from a 37 °C water bath for

seven days to ensure proper sizing after deflation. Once removed, it was found that two samples had ruptured balloons, one with a laceration on the entire length of the balloon (Figure 4.5A) and another with a small puncture hole in the balloon that was only visible when trying to inflate the balloon again. The surviving balloons took about 81 seconds to deflate—well below the allotted 15 minutes. After the two remaining balloons were deflated, an observable ridge formed on one of the balloons, while the other balloon appeared normal. When the tip and balloon regions were pushed through a Fr size gauge, it was found that all of the tips were able to pass through a 16 Fr hole, but all surviving ballons failed to pass through the maximum allowed 20 Fr gauge (average catheter shaft outer diameter was ~15.71 Fr post removal from water bath). The catheter without the ridge could pass through a 21 Fr hole, while the one with the ridge could not pass through a 22 Fr hole.

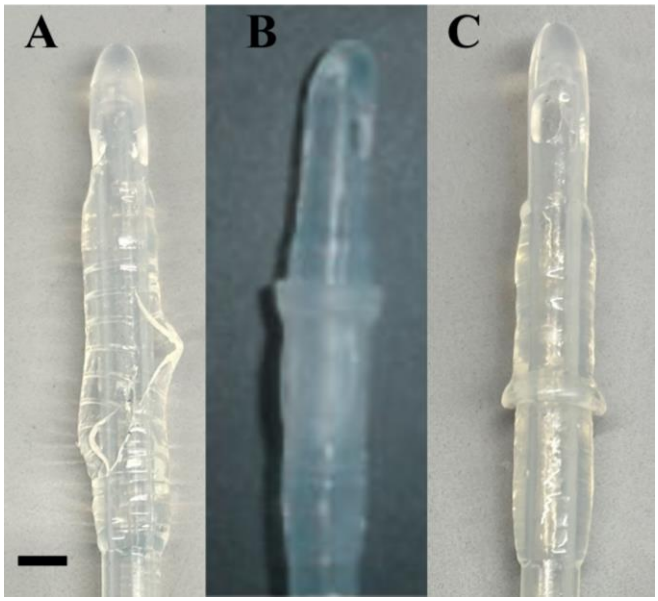

Figure 4.5. Damage to tested samples and the formation of balloon creep in all-silicone catheters.

(A) An image of the laceration in the balloon of a test sample following removal from the water bath. Images of the formation of a ridge in the balloon region of all-silicone catheters after submersion of the catheter (B) were observed by Parkin *et al.* (2002) and (C) in this work. Scale bar is four mm. Modified from Parkin *et al.* (2002).[104]

In unmodified all-silicone catheters, the development of small rings or cuffs on silicone balloons after the inflating water is drained, a phenomenon known as "creep" has been reported to occur occasionally both clinically with suprapubic catheterization and *in vitro* testing (Figure 4.5B).[104] Interestingly, this effect was reported to a lesser extent with other materials, such as hydrogel-coated latex. This incomplete deflation can cause increased difficulty in the removal and further trauma to host tissue. The silicone balloons on commercially available

catheters are fabricated by fixing the top and bottom of the balloon in place, creating a seal to allow for proper inflation from the syringe port lumen. The incorporation of silicone oil caused the expansion of the silicone balloon material, resulting in the generation of ridges in the balloon region, as seen in Figure 4.5C. Although this result constitutes a failure, it is essential to note that it has been observed in unmodified and modified catheters. These data suggest that using catheters fabricated from other materials could limit the formation of cuffs post-deflation.

4.2.2.6 Balloon Volume Maintenance

If balloon leakage occurs over time and reaches a critically low volume where the weight of a urine bag could cause balloon rupture or sudden slippage of the catheter, further trauma could be inflicted upon the patient's urinary system. To prevent this from happening, ensuring the retention of the inflating liquid within the catheter and balloon is essential. The balloons were filled with a methylene blue dye solution and placed over an indicator material, as described in section 4.1.2.5. Samples used in the deflation of reliability testing were taken and used for this experiment. Due to the rupture of two balloons, the remaining two test samples were used and had no presence of leakage over 24 hours, yielding passing results. The inconsistencies in the integrity of the balloons could be caused by variations in balloon shape, which could be caused by using a dish to infuse test samples.

4.3 Summary

Through rigorous testing, the performance of commercially manufactured urinary catheters has been investigated after full infusion of the shaft region with silicone oil. Completing the urinary catheter-specific ASTM F623-19 with slight modification allows for standardizing the performance of those devices that already exist and are currently used in patients. Infusing silicone oil into the all-silicone catheters led to some samples failing specific tests related to balloon integrity, as seen in Table 4.1. The variance in balloon shape, even when inflated with identical volumes, could have contributed to the results. Further, as similar survivability for inflation volumes of 14 mL and 16 mL were observed in resistance to pullout testing, completing tests where the balloons are inflated with 14 mL could prove beneficial. The high failure rates

in the tests where the catheters were submerged in liquid (resistance to rupture and deflation reliability tests) could be due to a combination of increased pressure on the inflation balloons and weakening of the silicone material from infusion when exposed to conditions meant to mimic the bladder environment. Further, the sudden change in temperature (~23 °C to 37 °C) could weaken the material, causing ruptures. With lower inflation volumes, the structural integrity of the balloon might be retained better, as there would likely be less pressure on the balloons. As this work tested a single brand and size of catheters across multiple manufacturing lots, further testing with different balloon inflation volumes, manufacturers, and Fr sizes would be beneficial. Still, due to the limited sample size of most tests, more testing must be completed to confirm that the results would represent a larger sample size and that different Fr sizes of catheters would perform similarly.

Table 4.1. Summary of ASTM F623-19 test results for infused all-silicone catheters.

Test	Passing Results	Failing Results	Notes
Inflated Balloon Response to Pullout	2	1	Failure occurred during rebound on impact load test.
Resistance to Rupture	1	3	One sample with a nonuniform balloon shape. Three ruptures within two hours of starting the test.
Deflation Reliability	0	4	Two failures from ruptures.
Balloon Volume Maintenance	2	0	The surviving test samples from the deflation reliability test were used.

CHAPTER 5

SILICONE-COATED LATEX INDWELLING CATHETERS

Due to the performance of the sectionally infused all-silicone catheters in modified ASTM F623-19 testing and the generation of a balloon cuff simply due to infusion, catheters manufactured from multiple materials could be explored to preserve functionality while also providing the antifouling ability that infused silicones offer. One promising type of catheter that has the potential is the silicone-coated latex (SCL) indwelling Foley catheter, where a silicone overlayer is adhered to the latex underlayer and fixed in place. In this chapter, Bard 16 Fr SCL catheters were fully infused with silicone oil to characterize the infusion process before subjecting them to ASTM F623-19 testing to compare performance to that of previously tested all-silicone materials.

5.1 Materials and Methods

ASTM F623-19 was used for functionality and performance testing of iSCL catheters. All test samples were Bard 16 Fr SCL Foley catheters infused with 20 cSt silicone oil for 120 hours. Once removed, excess oil was removed from the inner lumen and outer surface, as previously outlined. Catheters were then inflated with 10 mL of DI water and subjected to the respective testing procedures and conditions. The respective lot numbers for materials used in testing can be found in Appendix C.

5.1.1 Balloon Size and Shaft Size

A 3D-printed Fr size gauge was printed out of polylactic acid (PLA) filament, adhering to the outlined Fr size chart specified and tolerances in sections 3.1.2 and Annex 5.4.1 of ASTM F623-19 (2019). The same printer and methods were used to prepare the desired object, as described in section 3.1.4. Polylactic acid (PLA) filament (Overture) was used to print desired objects using a nozzle temperature of 215 °C and a build plate temperature of 60 °C. The layer height was 0.2 mm, and the infill was set to 15% in a gyroid pattern.

5.1.2 Inflated Balloon Response to Pullout

A borosilicate glass funnel (ULAB) with an internal shaft diameter of about nine mm was suspended in a ring stand (positioned at the table's edge) at the V-shaped region, mimicking the urethra and bladder outlet. For each test, the proximal end of the catheter was fed through the inner lumen of the funnel, where the balloon was inflated with 16 mL of DI water and allowed to rest on the inner surface of the V-shaped region of the funnel. A 454 g (one pound) weight was attached just above the Y splitter region of the catheter before testing. two tests were performed: 1) a two-minute static load test where the load was suspended from the end of the catheter, and 2) an impact load test where the weight attached to the catheter was lifted 0.6 meters above the natural static hanging point and subsequently dropped. Test failures were indicated by either balloon rupture or passage of the entire balloon (and, therefore, the whole catheter) through the barrel of the funnel.

5.1.3 Resistance to Rupture

Fully infused and control catheters were placed into a 1000 mL Pyrex glass beaker containing 750 mL of artificial urine with a pH of ~6.7 after inflating the balloons with 16 mL of DI water using a 10 mL syringe (Luer-lock, BD). The recipe for artificial urine is described in Appendix 3 of ASTM F623-19. The beaker was covered with tinfoil and incubated at 37.8 °C for seven days. Any catheters with burst balloons failed the test, and deflated balloons resulted in an invalid result.

5.1.4 Deflation Reliability

Test sample balloons were inflated through the inflation syringe port with DI water, submerged in a two-liter high-density polyethylene (HDPE) container of DI water, and placed into an incubator at 37.8 °C for seven days. The container was covered to prevent evaporation throughout testing. After seven days, catheters were removed from the DI water and drained by connecting a 10 mL syringe to the syringe port inflation valve or by cutting the catheter approximately 13 mm distal to the balloon if no drainage occurred into the syringe. Balloons were given 15 minutes to drain and had to be no greater than four Fr sizes (~1.32

mm) larger than the label Fr size to pass the test. Failures were determined by the inability to deflate or balloon greater than four Fr sizes larger than the label size after the draining period.

5.1.5 Balloon Volume Maintenance

The balloons of fully infused catheters were inflated with a 0.5 mg/mL solution of methylene blue (LC169407, LabChem) in DI water and placed on a cellulosic wipe to act as a visual indicator of leakage from the balloon. Test samples were covered with tinfoil to protect them from light throughout the 24-hour test duration. Failures were classified as discoloration of the indicator surface caused by dye leakage.

5.1.6 Statistical Analysis

Statistical analysis of data was conducted using GraphPad Prism, Version 10 (GraphPad Software). The statistical significance of the experiments was tested using Mann-Whitney tests. Significance values are: * = $p<0.05$, ** = $p<0.01$, *** = <0.001, **** = $p< 0.0001$.

5.2 Results and Discussion

5.2.1 Characterization of Infusion

The complete infusion of SCL catheters (iSCLs) with silicone oil resulted in the expansion of important parameters such as mass, silicone overlayer thickness, and length of the shaft region. The percentage increases were 0.97 (±0.07)%, 6.59 (±3.62)%, and 0.20 (±0.17)%, respectively. This correlated to the average iSCL Fr size after infusion, increasing from ~17.1 Fr to ~17.66 Fr. The latex underlayer allowed for expansion of the

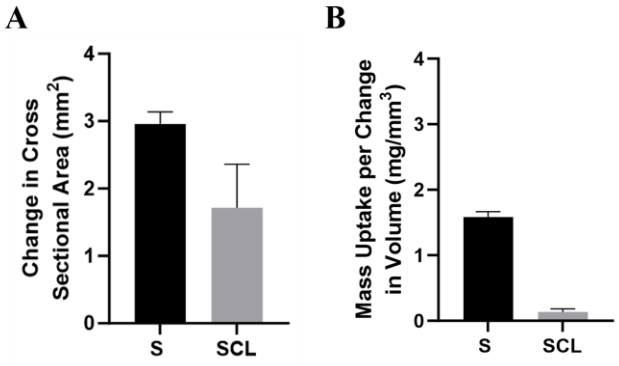

Figure 5.1. All-silicone and SCL matrix changes from infusion. Graphs of the (A) cross-sectional area and (B) mass uptake per change in volume comparisons for the shaft region all-silicone (S) and SCL catheters. In all graphs presented, the error bars are the standard deviation. Statistical significance between testing conditions was assessed using a Mann-Whitney test. Unless otherwise stated, comparisons were nonsignificant.

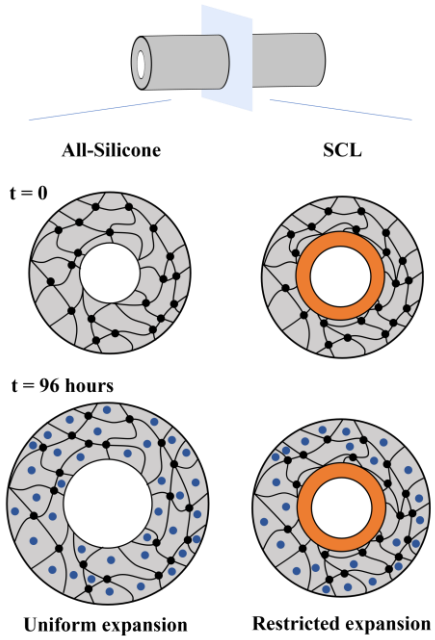

Figure 5.2. Schematic of the cross-sectional view of all-silicone and SCL catheter polymeric matrix changes due to infusion.

cross-sectional area (Figure 5.1A) but limited the extent of the increase in length (0–1 mm). However, there was no statistical difference in the change in the cross-sectional area (p=0.1). Compared to the percent increases in the mass, inner and outer diameter, and length of the shaft region of Bard 14 Fr catheters, there appear to be restricted increases in the volume of the materials, as depicted in Figure 5.1B. Again, with the change in mass per volume change, no significant difference was observed (p=0.1). Although other parameters increased, differences in factors such as the crosslinking ratio of the silicone or types of additives and filler materials used in SCLs compared to all-silicone could be different, thus contributing to the smaller changes in mass per volume change (Figure 5.2). It is hypothesized that this is due to the adhesive that bonds the latex and silicone layers together or from differences in the silicone matrix itself, limiting the ability of the matrix to swell uniformly.

5.3 Functionality Testing

The previously conducted ASTM F623-19 tests were repeated to test the functionality and durability of iSCLs. Due to the limited absorption of silicone oil into the silicone matrix, coupled with the adherence of the silicone material to the latex underlayer in the balloon region, iSCL balloons were inflated with 10 mL of water. The drainage flow rate and balloon and shaft size testing were not conducted to be consistent with the all-silicone testing undertaken previously. All other test methods and conditions remained the same.

5.3.1 Resistance To Pullout

The infused balloons retained shapes similar to controls, with the only observable difference being a slight change in the color. All three iSCL test samples passed the static and impact load testing when inflated with

the manufacturer's recommended volume of 10 mL. From the testing results, the infusion of silicone oil did not appear to compromise the structural integrity of the balloon, as all test samples passed both tests. Further, there was no delamination of the silicone layer from the latex underlayer, which could occur in a system containing infused PDMS.

5.3.2 Resistance to Rupture

Test samples were prepared for testing as outlined in section 5.1.3. All four samples survived testing and the balloons drained easily once a syringe was connected to the syringe port. These results, in contrast to those obtained for the infused all-silicone catheters, are hypothesized to be due to the limited expansion of the PDMS matrix that coats the latex underlayer. As the SCL balloons absorb far less silicone oil as the matrix expansion is restricted, the overall integrity of the balloon is weakened far less as the polymeric chains are placed under less stress. This likely leads to the retention of the structural integrity of the balloons throughout testing.

5.3.3 Deflation Reliability

To test the deflation reliability, we subjected four test samples to conditions outlined in section 5.1.4. Following the removal of test samples from the 37 °C DI bath after seven days, all four test samples deflated on demand without applied force through the syringe port. On average, it took 13.75 (±1.71) seconds for the balloons to deflate on their own fully. After infusion, the average Fr size was ~16.5 Fr for each 16 Fr SCL catheter. Although there was no formation of a cuff region in the balloon due to infusion as observed with all-silicone materials, once deflated after submersion in water for seven days, noticeable wrinkles in the balloons formed. This was also observed in all four unmodified SCL catheters subjected to the same treatment. Latex and other coated materials have a shaft tolerance of -1 to +2 Fr size compared to the label size. However, all successful test samples must pass through a calibrated Fr gauge hole no larger than four Fr sizes greater than the labeled size. This increase in outer diameter (~1.32 mm) indicates that slight increases in the balloon region size after use are expected. The deflated balloon region of all four catheters could be threaded through either the 19 or 20-Fr size gauge of a 3D printed Fr gauge calibration tool, which

indicates a passing result. Despite being placed in an HDPE container—one of the recommended container materials listed in ASTM F623-19 documentation to prevent sample damage—the exterior of all four tested samples slightly changed color from dark orange to pale tan after testing.

5.3.4 Balloon Volume Maintenance

The balloons of all four iSCL catheters from deflation reliability were tested using methods outlined in section 5.1.5. No indicator dye was visible on the indicator surfaces, demonstrating no leakage of the inflating volume in any test samples, indicating that all four samples passed the specified test. The limited expansion of balloon material due to infusion likely causes less stress to be placed on the balloons once removed from the oil bath and, therefore, likely does not cause leakage when being tested.

5.4 Summary

Compared to the all-silicone catheters tested, the obtained data suggest that iSCLs are a potential option for the aftermarket application of the silicone oil coating without sacrificing the structural integrity of essential components, such as the balloon. This was demonstrated through the performance of the iSCL catheters compared to all-silicone catheters when subjected to ASTM F623-19 testing (Table 5.1). Further investigation should be conducted into the antifouling performance of iSCLs to determine if it can be an effective solution, just as infused all-silicone catheters have been demonstrated to be through either benchtop testing or in a mouse model, as was conducted with silicone materials.

Table 5.1. Summary of ASTM F623-19 test results for iSCL catheters.

Test	Passing Results	Failing Results	Notes
Inflated Balloon Response to Pullout	3	0	
Resistance to Rupture	4	0	
Deflation Reliability	4	0	
Balloon Volume Maintenance	4	0	Slight discoloration of test samples.

Chapter 6

APPLICATIONS AND CONCLUSIONS

6.1 Summary

As previously described in Chapter 1, millions of urinary catheters are used each year to treat problems related to urinary retention or incontinence.[9] However, the risk of developing CAUTI remains high due to host protein deposition, such as fibrinogen, on the catheter shortly after insertion.[4,31,45,46,48] These proteins enable pathogenic adherence and subsequent biofilm formation and infection.[8,36,40] The effectiveness of liquid-infused silicone catheters in reducing pathogenic adhesion to the underlying substrate has been demonstrated *in vitro*[45,64,66,67] and *in vivo* through a CAUTI mouse model.[45] Still, many hurdles remain before it can be approved for human use.

This work has further characterized these materials to better quantify important changes in material properties due to liquid infusion. The successful completion of an entrepreneurship training program and the subsequent exploration of the regulatory approval process for urinary catheters have yielded crucial insights essential for translating this technology to the market. This research has characterized the infusion of commercial catheters and identified consistent time-dependent increases in measured parameters such as mass, length, and inner and outer diameter when infusing silicone oil into fabricated PDMS samples and silicone catheters. To further understand the system, the height of the oil overlayer that provides the material's antifouling abilities was examined using confocal imaging. It was discovered that fully infused samples had heights of 56.51 μm, which could be reduced through mechanical removal of excess oil to 5 μm–29.3 μm. The fully infused blotted surfaces demonstrated heterogeneity due to oil pooling, so the true oil overlayer height and the corresponding amount of silicone oil on the surface of a catheter are likely lower than reported here and are closer to those reported in literature.[62,63] The weakening of the polymeric matrix due to infusion was quantified through the Shore hardness of partially and fully infused materials. Notably, significant increases in the intensity of the oil channel corresponded with a substantial reduction in the hardness of the material in the same infusion range. Additionally, the intensity of the liquid channel

in the partial and complete infusions provided valuable insights into the distribution and presence of oil in the polymeric network, which warrants further investigation.

Functionality testing displayed that the infusion of silicone oil can negatively impact the structural integrity of the balloon, which severely limits the longevity of use of the device. Due to the mixed results obtained in standardized testing of infused silicone catheters, iSCLs were also investigated. These devices experienced limited parameter changes and uptake in oil and performed well during standardized testing. An investigation of the functionality testing of partially infused all-silicone catheters should be conducted to compare their performance. In comparison, the iSCL samples passed all tests and saw little to no reductions in functionality due to infusion. This is likely due to the limited parameter changes due to infusion when compared to the all-silicone counterparts. Without determination of the antifouling ability of iSCLs, it remains unclear if the amount of oil absorbed is enough to provide antifouling properties to the catheters. However, further standardized testing and assessment of antifouling ability for a wider range of brands and sizes of all-silicone and SCL catheters will prove beneficial for translating this technology to the market.

6.2 Applications and Future Directions

Understanding how the treated commercial catheters interact with the host bladder and urethral tissue over a standard use cycle is crucial. Similarly, influences on intermittent urine flow and the integrity of the oil overlayer (depending on the fabrication method) should also be investigated. Conducting a clinical trial will be essential for further transitioning this technology to the market by comparing CAUTI incidence rates to the current gold standard. To prepare for clinical trials, methods for reducing the oil overlayer further than blotting alone could be through the partial infusions of commercial catheters or complete stripping of the oil overlayer by rinsing with water. However, it is unknown if this could prevent proper antifouling performance over time if the oil layer is removed through contact with host tissue or removal from intermittent urine flow.

Incorporating additional components into the catheter could prove beneficial to ensure sustained antifouling performance. In PDMS-based systems infused with silicone oil, embedded vasculature—channels formed within the bulk matrix—has demonstrated enhanced replenishment of the liquid overlayer to sustain antifouling performance *in vitro*.[64] In agar-based models, the inhibition of *E. coli* growth can be controlled through the diffusion of antibiotics, such as gentamicin, from embedded channels to the surface.[105] Alternatively, bacterial growth on the surface has been monitored through the diffusion of metabolites from the surface to a carrier fluid contained in buried channels,[106] highlighting the capabilities of this method. To replicate this in commercial urinary catheters, vasculature could be fabricated into bulk material during manufacturing, or the third lumen present in some models of Foley catheters for bladder irrigation could be utilized for this purpose.[102] Taken together, embedded channels could act as silicone oil reservoirs to diffuse additional oil to the surface to replenish defects in the oil overlayer, preserve antifouling ability over time, and provide pathways to diffuse hydrophobic antibiotics effectively if needed.

REFERENCES

1. Gordon Betts, J. *et al.* Gross Anatomy of Urinary Transport. in *Anatomy and Physiology* (Openstax, 2022).

2. National Institute of Diabetes and Digestive and Kidney Diseases. *The Urinary Tract and How It Works.* Available at: https://www.niddk.nih.gov/health-information/urologic-diseases/urinary-tract-how-it-works (2020).

3. Feneley, R. C. L., Hopley, I. B. & Wells, P. N. T. Urinary Catheters: History, Current Status, Adverse Events and Research Agenda. *J. Med. Eng. Technol.* **39**, 459–470 (2015).

4. Andersen, M. J. & Flores-Mireles, A. L. Urinary Catheter Coating Modifications: The Race against Catheter-Associated Infections. *Coatings* **10**, 23 (2019).

5. Singha, P., Locklin, J. & Handa, H. A Review of the Recent Advances in Antimicrobial Coatings for Urinary Catheters. *Acta Biomater.* **50**, 20–40 (2017).

6. Gould, C. V., Umscheid, C. A., Agarwal, R. K., Kuntz, G. & Pegues, D. A. Guideline for Prevention of Catheter-Associated Urinary Tract Infections (2009). (2019).

7. Chenoweth, C. E., Gould, C. V. & Saint, S. Diagnosis, Management, and Prevention of Catheter-Associated Urinary Tract Infections. *Infect. Dis. Clin. North Am.* **28**, 105–119 (2014).

8. Lo, E. *et al.* Strategies to Prevent Catheter-Associated Urinary Tract Infections in Acute Care Hospitals: 2014 Update. *Infect. Control Hosp. Epidemiol.* **35**, 464–479 (2014).

9. Saint, S. *et al.* Are physicians Aware of Which of Their Patients Have Indwelling Urinary Catheters? *Am. J. Med.* **109**, 476–480 (2000).

10. Fong, C. K. Exploration of Liquid-Infused Urinary Catheters: Fabrication, Functionality, and Liquid Loss. (University of Maine, 2024).

11. Van Doorn, T., Berendsen, S. A., Scheepe, J. R. & Blok, B. F. M. Single Use Versus Reusable Catheters in Intermittent Catheterisation for Treatment of Urinary Retention: a Protocol for a Multicentre, Prospective, Randomised Controlled, Non-Inferiority Trial (COMPaRE). *BMJ Open* **12**, e056649 (2022).

12. Ahluwalia, R. *et al.* The Surgical Risk of Suprapubic Catheter Insertion and Long-Term Sequelae. *Ann. R. Coll. Surg. Engl.* **88**, 210–213 (2006).

13. Lee, C., Gill, B. C., Vasavada, S. P. & Rackley, R. R. Does Size Matter? Measured and Modeled Effects of Suprapubic Catheter Size on Urinary Flow. *Urology* **102**, 266.e1-266.e5 (2017).

14. Temenoff, J. S. & Mikos, A. G. *Biomaterials: The Intersection of Biology and Materials Science*. (Pearson).

15. Shanks, R. A. & Kong, I. General Purpose Elastomers: Structure, Chemistry, Physics and Performance. in *Advances in Elastomers I* (eds. Visakh, P. M., Thomas, S., Chandra, A. K. & Mathew, Aji. P.) vol. 11 11–45 (Springer Berlin Heidelberg, Berlin, Heidelberg, 2013).

16. Brown, T., LeMay, H. & Bursten, B. Modern Materials. in *Chemistry: The Central Science* (Prentice Hall, 2000).

17. Flores, J. M., Gallardo, A. K. R., Barba, B. J. D. & Tranquilan-Aranilla, C. Effect of Ionizing Radiation on the Physicochemical and Functional Properties of Silicone Rubber and Silicone Foley Catheter. *Radiat. Phys. Chem.* **216**, 111356 (2024).

18. Van Den Berg, D., Asker, D., Awad, T. S., Lavielle, N. & Hatton, B. D. Mechanical Deformation of Elastomer Medical Devices Can Enable Microbial Surface Colonization. *Sci. Rep.* **13**, 7691 (2023).

19. Hao, P., Wang, Y., Sun, X., Wang, J. & Zhang, L. W. Derivation of the Toxicological Threshold of Silicon Element in the Extractables and Leachables from the Pharmaceutical Packaging and Process Components. *Toxicol. Ind. Health* **38**, 819–834 (2022).

20. Mojsiewicz-Pieńkowska, K. Size exclusion chromatography with evaporative light scattering detection as a method for speciation analysis of polydimethylsiloxanes. III. Identification and determination of dimeticone and simeticone in pharmaceutical formulations. *J. Pharm. Biomed. Anal.* **58**, 200–207 (2012).

21. Brook, M. A. The chemistry and physical properties of biomedical silicones. in *Biomaterials in Plastic Surgery* 52–67 (Elsevier, 2012). doi:10.1533/9780857096418.52.

22. Klevens, R. M. *et al.* Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002. *Public Health Rep.* **122**, 160–166 (2007).

23. Lo, J., Lange, D. & Chew, B. Ureteral Stents and Foley Catheters-Associated Urinary Tract Infections: The Role of Coatings and Materials in Infection Prevention. *Antibiotics* **3**, 87–97 (2014).

24. Goudie, A. *et al.* Costs of Venous Thromboembolism, Catheter-Associated Urinary Tract Infection, and Pressure Ulcer. *Pediatrics* **136**, 432–439 (2015).

25. Hollenbeak, C. S. & Schilling, A. L. The Attributable Cost of Catheter-Associated Urinary Tract Infections in the United States: A Systematic Review. *Am. J. Infect. Control* **46**, 751–757 (2018).

26. Kandilov, A., Coomer, N. & Dalton, K. The Impact of Hospital-Acquired Conditions on Medicare Program Payments. *Medicare Medicaid Res. Rev.* **4**, E1–E23 (2014).

27. Yi, S. H., Baggs, J., Gould, C. V., Scott, R. D. & Jernigan, J. A. Medicare Reimbursement Attributable to Catheter-associated Urinary Tract Infection in the Inpatient Setting: A Retrospective Cohort Analysis. *Med. Care* **52**, 469–478 (2014).

28. Lederer, J. W., Jarvis, W. R., Thomas, L. & Ritter, J. Multicenter Cohort Study to Assess the Impact of a Silver-Alloy and Hydrogel-Coated Urinary Catheter on Symptomatic Catheter-Associated Urinary Tract Infections. *J. Wound. Ostomy Continence Nurs.* **41**, 473–480 (2014).

29. Letica-Kriegel, A. S. *et al.* Identifying the Risk Factors for Catheter-Associated Urinary Tract Infections: a Large Cross-Sectional Study of Six Hospitals. *BMJ Open* **9**, e022137 (2019).

30. Tambyah, P. A. & Maki, D. G. Catheter-Associated Urinary Tract Infection Is Rarely Symptomatic: A Prospective Study of 1497 Catheterized Patients. *Arch. Intern. Med.* **160**, (2000).

31. Flores-Mireles, A., Hreha, T. N. & Hunstad, D. A. Pathophysiology, Treatment, and Prevention of Catheter-Associated Urinary Tract Infection. *Top. Spinal Cord Inj. Rehabil.* **25**, 228–240 (2019).

32. Hooton, T. M. *et al.* Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin. Infect. Dis.* **50**, 625–663 (2010).

33. National Healthcare Safety Network. *Urinary Tract Infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection [UTI]) Events*. Available at: www.cdc.gov/nhsn/pdfs/pscmanual/7psccauticurrent.pdf (2024).

34. Phillips, C. D. *et al.* Asymptomatic Bacteriuria, Antibiotic Use, and Suspected Urinary Tract Infections in Four Nursing Homes. *BMC Geriatr.* **12**, 73 (2012).

35. Podkovik, S. *et al.* Prevalence of Catheter-Associated Urinary Tract Infections in Neurosurgical Intensive Care Patients – The Overdiagnosis of Urinary Tract Infections. *Cureus* (2019).

36. Trautner, B. W. & Darouiche, R. O. Role of biofilm in catheter-associated urinary tract infection. *Am. J. Infect. Control* **32**, 177–183 (2004).

37. Weiner, L. M. *et al.* Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014.

38. Saint, S. & Chenoweth, C. E. Biofilms and Catheter-Associated Urinary Tract Infections. *Infect. Dis. Clin. North Am.* **17**, 411–432 (2003).

39. Raz, R., Schiller, D. & Nicolle, L. E. Chronic Indwelling Catheter Replacement Before Antimicrobial Therapy for Symptomatic Urinary Tract Infection.

40. Stewart, P. S. & William Costerton, J. Antibiotic resistance of bacteria in biofilms. *The Lancet* **358**, 135–138 (2001).

41. Rutherford, S. T. & Bassler, B. L. Bacterial Quorum Sensing: Its Role in Virulence and Possibilities for Its Control. *Cold Spring Harb. Perspect. Med.* **2**, a012427–a012427 (2012).

42. Martinez, J. J. Type 1 Pilus-Mediated Bacterial Invasion of Bladder Epithelial Cells. *EMBO J.* **19**, 2803–2812 (2000).

43. Hunstad, D. A., Justice, S. S., Hung, C. S., Lauer, S. R. & Hultgren, S. J. Suppression of Bladder Epithelial Cytokine Responses by Uropathogenic *Escherichia coli*. *Infect. Immun.* **73**, 3999–4006 (2005).

44. Justice, S. S., Hunstad, D. A., Seed, P. C. & Hultgren, S. J. Filamentation by *Escherichia coli* Subverts Innate Defenses During Urinary Tract Infection. *Proc. Natl. Acad. Sci.* **103**, 19884–19889 (2006).

45. Andersen, M. J. *et al.* Inhibiting Host-Protein Deposition on Urinary Catheters Reduces Associated Urinary Tract Infections. *eLife* **11**, e75798 (2022).

46. Flores-Mireles, A. L., Pinkner, J. S., Caparon, M. G. & Hultgren, S. J. EbpA Vaccine Antibodies Block Binding of *Enterococcus faecalis* to Fibrinogen to Prevent Catheter-Associated Bladder Infection in Mice. *Sci. Transl. Med.* **6**, (2014).

47. Budzynski, A. Z. & Shainoff, J. R. Fibrinogen and fibrin: Biochemistry and pathophysiology. *Crit. Rev. Oncol. Hematol.* **6**, 97–146 (1986).

48. Flores-Mireles, A. L. *et al.* Fibrinogen Release and Deposition on Urinary Catheters Placed during Urological Procedures. *J. Urol.* **196**, 416–421 (2016).

49. Umscheid, C. A. *et al.* Estimating the Proportion of Healthcare-Associated Infections That Are Reasonably Preventable and the Related Mortality and Costs. *Infect. Control Hosp. Epidemiol.* **32**, 101–114 (2011).

50. Desai, D. G., Liao, K. S., Cevallos, M. E. & Trautner, B. W. Silver or Nitrofurazone Impregnation of Urinary Catheters Has a Minimal Effect on Uropathogen Adherence. *J. Urol.* **184**, 2565–2571 (2010).

51. Kunin, C. M., Chin, Q. F. & Chambers, S. Formation of Encrustations on Indwelling Urinary Catheters in the Elderly: A Comparison of Different types of Catheter Materials in "Blockers" and "Nonblockers". *J. Urol.* **138**, 899–902 (1987).

52. Noimark, S., Dunnill, C. W., Wilson, M. & Parkin, I. P. The Role of Surfaces in Catheter-Associated Infections. *Chem. Soc. Rev.* **38**, 3435 (2009).

53. Ahmed, E. M. Hydrogel: Preparation, Characterization, and Applications: A review. *J. Adv. Res.* **6**, 105–121 (2015).

54. Talja, M., Korpela, A. & Järvi, K. Comparison of Urethral Reaction to Full Silicone, Hydrogen-coated and Siliconised Latex Catheters. *Br. J. Urol.* **66**, 652–657 (1990).

55. Kazmierska, K. A., Thompson, R., Morris, N., Long, A. & Ciach, T. In Vitro Multicompartmental Bladder Model for Assessing Blockage of Urinary Catheters: Effect of Hydrogel Coating on Dynamics of Proteus mirabilis Growth. *Urology* **76**, 515.e15-515.e20 (2010).

56. Zhu, Z., Wang, Z., Li, S. & Yuan, X. Antimicrobial Strategies for Urinary Catheters. *J. Biomed. Mater. Res. A* **107**, 445–467 (2019).

57. Pickard, R. *et al.* Types of Urethral Catheter for Reducing Symptomatic Urinary Tract Infections in Hospitalised Adults Requiring Short-Term Catheterisation: Multicentre Randomised Controlled Trial and Economic Evaluation of Antimicrobial-and Antiseptic-Impregnated Urethral Catheters (the CATHETER trial). *Health Technol. Assess.* **16**, (2012).

58. Pickard, R. *et al.* Antimicrobial Catheters for Reduction of Symptomatic Urinary Tract Infection in Adults Requiring Short-Term Catheterisation in Hospital: a Multicentre Randomised Controlled Trial. *The Lancet* **380**, 1927–1935 (2012).

59. Karchmer, T. B., Giannetta, E. T., Muto, C. A., Strain, B. A. & Farr, B. M. A Randomized Crossover Study of Silver-Coated Urinary Catheters in Hospitalized Patients. *Arch. Intern. Med.* **160**, 3294 (2000).

60. Kilonzo, M., Vale, L., Pickard, R., Lam, T. & N'Dow, J. Cost Effectiveness of Antimicrobial Catheters for Adults Requiring Short-term Catheterisation in Hospital. *Eur. Urol.* **66**, 615–618 (2014).

61. Applebee, Z. & Howell, C. Multi-Component Liquid-Infused Systems: a New Approach to Functional Coatings. *Ind. Chem. Mater.* 10.1039.D4IM00003J (2024).

62. Fong, C. K. *et al.* Removal of Free Liquid Layer from Liquid-Infused Catheters Reduces Silicone Loss into the Environment while Maintaining Adhesion Resistance. Preprint at https://doi.org/10.1101/2023.09.14.23295548 (2023).

63. Lavielle, N., Asker, D. & Hatton, B. D. Lubrication Dynamics of Swollen Silicones to Limit Long Term Fouling and Microbial Biofilms. *Soft Matter* **17**, 936–946 (2021).

64. Howell, C. *et al.* Self-Replenishing Vascularized Fouling-Release Surfaces. *ACS Appl. Mater. Interfaces* **6**, 13299–13307 (2014).

65. Kovalenko, Y. *et al.* Bacterial Interactions with Immobilized Liquid Layers. *Adv. Healthc. Mater.* **6**, 1600948 (2017).

66. MacCallum, N. *et al.* Liquid-Infused Silicone As a Biofouling-Free Medical Material. *ACS Biomater. Sci. Eng.* **1**, 43–51 (2015).

67. Regan, D. P. *et al.* Combining the Geometry of Folded Paper with Liquid-Infused Polymer Surfaces to Concentrate and Localize Bacterial Solutions. *Biointerphases* **14**, 041005 (2019).

68. Howell, C., Grinthal, A., Sunny, S., Aizenberg, M. & Aizenberg, J. Designing Liquid-Infused Surfaces for Medical Applications: A Review. *Adv. Mater.* **30**, 1802724 (2018).

69. Howell, C. *et al.* Stability of Surface-Immobilized Lubricant Interfaces under Flow. *Chem. Mater.* **27**, 1792–1800 (2015).

70. Juthani, N. *et al.* Infused Polymers for Cell Sheet Release. *Sci. Rep.* **6**, 26109 (2016).

71. Flory, P. J. Statistical Mechanics of Swelling of Network Structures. *J. Chem. Phys.* **18**, 108–111 (1950).

72. Flory, P. J. & Rehner, J. Statistical Mechanics of Cross-Linked Polymer Networks II. Swelling. *J. Chem. Phys.* **11**, 521–526 (1943).

73. Sotiri, I. *et al.* Tunability of Liquid-Infused Silicone Materials for Biointerfaces. *Biointerphases* **13**, 06D401 (2018).

74. Gedde, U. W., Hellebuych, A. & Hedenqvist, M. Sorption of low molar mass silicones in silicone elastomers. *Polym. Eng. Sci.* **36**, 2077–2082 (1996).

75. Rushton, A., Ward, A. S. & Holdich, R. G. Fluid Flow Through Porous Media. in *Solid-Liquid Filtration and Separation Technology* (Wiley).

76. Chisholm, C. F. *et al.* In Vivo Analysis of the Potency of Silicone Oil Microdroplets as Immunological Adjuvants in Protein Formulations. *J. Pharm. Sci.* **104**, 3681–3690 (2015).

77. Krayukhina, E. *et al.* An Assessment of the Ability of Submicron- and Micron-Size Silicone Oil Droplets in Dropped Prefillable Syringes to Invoke Early- and Late-Stage Immune Responses. *J. Pharm. Sci.* **108**, 2278–2287 (2019).

78. Melo, G. B. *et al.* Silicone Oil-Free Syringes, Siliconized Syringes and Needles: Quantitative Assessment of Silicone Oil Release with Drugs Used for Intravitreal Injection. *Acta Ophthalmol. (Copenh.)* **99**, (2021).

79. Liu, J., Ronk, M., Fujimori, K., Lee, H. & Nashed-Samuel, Y. Analysis of Silicone Oil in Prefilled Syringes and Biopharmaceutical Drug Products Using High-Performance Liquid Chromatography. *AAPS PharmSciTech* **22**, 75 (2021).

80. Uchino, T., Miyazaki, Y., Yamazaki, T. & Kagawa, Y. Immunogenicity of Protein Aggregates of a Monoclonal Antibody Generated by Forced Shaking Stress with Siliconized and Nonsiliconized Syringes in BALB/c Mice. *J. Pharm. Pharmacol.* **69**, 1341–1351 (2017).

81. Narins, R. S. & Beer, K. Liquid Injectable Silicone: A Review of Its History, Immunology, Technical Considerations, Complications, and Potential: *Plast. Reconstr. Surg.* **118**, 77S-84S (2006).

82. Chan, Y. K., Cheung, N., Chan, W. S. C. & Wong, D. Quantifying Silicone Oil Emulsification in Patients: Are We Only Seeing the Tip of the Iceberg? *Graefes Arch. Clin. Exp. Ophthalmol.* **253**, 1671–1675 (2015).

83. Schwartz, S., Vaziri, K., Kishor, K. & Flynn, H. Tamponade in the Surgical Management of Retinal Detachment. *Clin. Ophthalmol.* 471 (2016) doi:10.2147/OPTH.S98529.

84. Sacha, G. A., Saffell-Clemmer, W., Abram, K. & Akers, M. J. Practical Fundamentals of Glass, Rubber, and Plastic Sterile Packaging Systems. *Pharm. Dev. Technol.* **15**, 6–34 (2010).

85. Pande, P. S., Neuman, R. P. & Cavanagh, R. R. *The Six Sigma Way Team Fieldbook: An Implementation Guide for Process Improvement Teams*. (McGraw-Hill, 2002).

86. Cai, Z., Skabeev, A., Morozova, S. & Pham, J. T. Fluid Separation and Network Deformation in Wetting of Soft and Swollen surfaces. *Commun. Mater.* **2**, 21 (2021).

87. Cai, Z. & Pham, J. T. How Swelling, Cross-Linking, and Aging Affect Drop Pinning on Lubricant-Infused, Low Modulus Elastomers. *ACS Appl. Polym. Mater.* **4**, 3013–3022 (2022).

88. Johnston, I. D., McCluskey, D. K., Tan, C. K. L. & Tracey, M. C. Mechanical Characterization of Bulk Sylgard 184 for Microfluidics and Microengineering. *J. Micromechanics Microengineering* **24**, 035017 (2014).

89. Ramesh, P., Joseph, R. & Sunny, M. C. A Comparative Evaluation of Coefficient of Friction and Mechanical Properties of Commercially Available Foley Catheters. *J. Biomater. Appl.* **15**, 344–350 (2001).

90. Ramstedt, M. *et al.* Evaluating Efficacy of Antimicrobial and Antifouling Materials for Urinary Tract Medical Devices: Challenges and Recommendations. *Macromol. Biosci.* **19**, 1800384 (2019).

91. Curtis, J. & Klykken, P. A Comparative Assessment of Three Common Catheter Materials. *Dow Corning Corp.* (2008).

92. Opperhuizen, A., Damen, H. W. J., Asyee, G. M., Van Der Steen, J. M. D. & Hutzinger, O. Uptake and elimination by fish of polydimethylsiloxanes (silicones) after dietary and aqueous exposure. *Toxicol. Environ. Chem.* **13**, 265–285 (1987).

93. Liu, M., Sun, J. & Chen, Q. Influences of Heating Temperature on Mechanical Properties of Polydimethylsiloxane. *Sens. Actuators Phys.* **151**, 42–45 (2009).

94. Sales, F. C. P., Ariati, R. M., Noronha, V. T. & Ribeiro, J. E. Mechanical Characterization of PDMS with Different Mixing Ratios. *Procedia Struct. Integr.* **37**, 383–388 (2022).

95. Dow Chemical Company. SYLGARD 184 Silicone Elastomer. (2017).

96. Hendlin, K., Meyers, J. & Monga, M. Foley Catheter Characteristics: Predicting Problems. *J. Endourol.* **23**, 169–172 (2009).

97. Campeau, M.-A. *et al.* Effect of Manufacturing and Experimental Conditions on the Mechanical and Surface Properties of Silicone Elastomer Scaffolds Used in Endothelial Mechanobiological Studies. *Biomed. Eng. OnLine* **16**, 90 (2017).

98. ASTM D2240-15: Test Method for Rubber Property Durometer Hardness. (2021).

99. Guerrero-Vaca, G., Rodríguez-Alabanda, Ó., Ibáñez-Ibáñez, P. F. & Rodríguez-Valverde, M. Á. Advances in Lubricated Polydimethylsiloxane Surfaces for Polyurethane Foam Molding. *J. Appl. Polym. Sci.* **139**, e53040 (2022).

100. Ariati, R., Sales, F., Souza, A., Lima, R. A. & Ribeiro, J. Polydimethylsiloxane Composites Characterization and Its Applications: A Review. *Polymers* **13**, 4258 (2021).

101. Ibáñez-Ibáñez, P. F., Montes Ruiz-Cabello, F. J., Cabrerizo-Vílchez, M. A. & Rodríguez-Valverde, M. A. Mechanical Durability of Low Ice Adhesion Polydimethylsiloxane Surfaces. *ACS Omega* **7**, 20741–20749 (2022).

102. ASTM F623-19: Performance Specification for Foley Catheter. (2019).

103. Chrisp, J. M. & Nacey, J. N. Foley Catheter Balloon Puncture and the Risk of Free Fragment Formation. *Br. J. Urol.* **66**, 500–502 (1990).

104. Parkin, J. *et al.* Urinary Catheter 'Deflation Cuff' Formation: Clinical Audit and Quantitative *In Vitro* Analysis. *BJU Int.* **90**, 666–671 (2002).

105. Marquis, K. *et al.* Vascularized Polymers Spatially Control Bacterial Cells on Surfaces. *Adv. Biosyst.* **4**, 1900216 (2020).

106. Dixon, B., Sui, C., Briley, A., Hsu, P.-C. & Howell, C. Continuous, Nondestructive Detection of Microorganism Growth at Buried Interfaces with Vascularized Polymers. *ACS Appl. Bio Mater.* **6**, 519–528 (2023).

APPENDIX A: LIST OF OPEN-ENDED QUESTIONS IN CUSTOMER DISCOVERY

Chapter 2 described what was learned from the technology transfer and entrepreneurial training. An essential aspect of this process entailed interviewing customers and stakeholders. As urinary catheters are necessary for treating a sizeable portion of patients that healthcare facilities treat in a wide range of departments, healthcare professionals were interviewed to determine the shortcomings of existing products. Below are sample questions that were asked during customer and stakeholder discovery interviews:

What does your typical day consist of?

How often do you deal with patients that require catheterization?

Of those patients what percentage would you say experience CAUTI?

What additional treatments are required with CAUTI?

How much stress is added to hospital resources with CAUTI?

What are some solutions you have tried to prevent CAUTI?

Do you have any catheter model type you prefer to use?

What do you like about Model X?

What do you dislike about Model X?

What are your thoughts on implementing new medical devices?

Who oversees purchasing the medical supplies for your department?

Where do you get these products now?

Do all departments use the same catheter?

Who else would you recommend I talk to?

Would you be willing to touch base again down the road?

APPENDIX B: EXPANDED TENSILE TESTING RESULTS

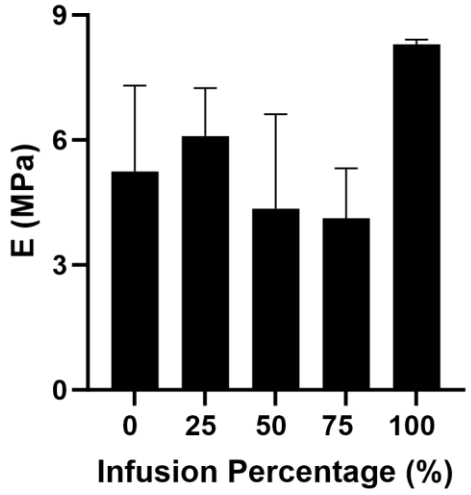

Figure B.1. Tensile testing results obtained from the full range of percent infusions tested in this work.

APPENDIX C: ADDITIONAL INFORMATION ON COMMERCIAL CATHETER INFUSION

Table C.1. Commercial catheter and infusing silicone oil lot numbers

Material	Manufacturer	Lot Number(s)
Bardia All-Silicone Two-Way, 14 Fr	CR Bard	NGHQ0277 NGHW0829 NGHY2552 NGHZ0279 NGJN3052
SelectSilicone 100% Silicone Foley catheters	Medline Industries	28722120001
Bardia All-Silicone Two-Way, 18 Fr	CR Bard	NGGZ0714
Dover Adult silicone 2-way catheter, 18Fr	Covidien	2226232
Bardia Silicone-Elastomer Coated Latex Foley catheters	CR Bard	MYHT3242
20 cSt Silicone Oil	Gelest	0082659942 1G-38878

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Evan Leonard was born in Portland, Maine, in August 2001. He was raised in Portland, Maine, and graduated from Deering High School in 2019. Evan went on to receive his Bachelor of Science in Biomedical Engineering from the University of Maine in 2023. After graduation, he will pursue a career in industry. Evan is a candidate for the Master of Science degree in Biomedical Engineering from the University of Maine in August 2024.