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Slippery lubricant-infused surfaces with anti-fouling and antimicrobial properties for preventing biofouling in biomedical applications

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With the annual surge in hospital admissions, the demand for medical treatment, whether invasive or non-invasive, remains constant. While the non-invasive treatments have less severe risks associated with them as opposed to invasive treatments, bacterial infections and improperly implanted device function, such as infection or occlusion of intravenous catheters, are shared concerns among the treatments. Therefore, research has been conducted to modify medical-grade polymers to enable more effective antibacterial and anti-fouling activities. This includes physical modifications to the surface of the material to induce contact bacterial killing and physical removal of biofouling agents through slippery surfaces. However, not all slippery surfaces are created equal. This review aims to assess the scope, efficacy, and limitations of existing strategies to guide the development of more biocompatible materials for medical applications.

1. Introduction

Many people will experience some form of medical treatment throughout their lives, whether a topical treatment, drug delivery, or temporary/permanent implanted device. The risks associated with medical treatments span a broad spectrum, ranging from minimal to significant, with the potential for morbidity and mortality.[1] Implanted medical devices, such as in-dwelling catheters, have many complications associated with them that can degrade the integrity and efficacy of the device. These complications pose one of the most serious threats to human health in the form of potential infections,

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occlusions, thrombosis, and general biofouling, which can prevent the proper functionality of the device and lead to prolonged hospital stays and increased treatment costs.

For example, bacterial infections in implanted devices can arise from multiple sources, including contamination at the site of implantation from the patient's skin and contamination within the device during implantation or subsequent treatment due to non-aseptic techniques. Hospital-acquired infections (HAIs), infections that occur at the time of treatment and were absent before hospital admission due to exposure to bacteria such as Gram-positive *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*) and Gram-negative *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), are a large cause of more intensive medical treatments, extended hospital stays, and financial burden on patients.[2,3] According to a 2015 study, 3.2% of hospitalized patients in the United States had at least one HAI, which equated to 633 300 patients.[2] Among hospitalized patients who require surgery, 2–5% of them develop skin and soft tissue infections (SSI) approximately 30 days after surgery or 90 days after medical device implantation,[2] resulting in a cost of approximately $10 443 to $25 546 per infection.[3–5]

While preventing infection altogether is ideal, infections are almost inevitable and must be treated efficiently and effectively. Several methods are currently used with varying degrees of invasiveness and success (Fig. 1A). In this context, a less invasive treatment method for an infected device would not involve surgical intervention to treat the infection. On the other hand, the more invasive alternative would be surgical removal and/or replacement. For example, one of the less invasive strategies to combat infections in implanted catheters is to flush or lock the catheter at the external end with a saline solution or an antibiotic solution. The "locked" solution could remain in the catheter anywhere from 2 minutes to 48 hours.[6] However, during this time, the potential for the solution to leak into the bloodstream remains a concern due to systemic toxicity, catheter degradation, and increased risk of occlusion.[7] Another less invasive method to treat infections is the systemic administration of antibiotics. Antibiotics, by definition, refer to a chemical substance derived from microorganisms that inhibit microbial growth and activity.[8,9] While antibiotics may be effective against bacterial infections to an extent, they are less likely to effectively inhibit bacterial growth over long periods due to antibiotic resistance, which is the ability of bacteria to adapt to an antibiotic environment and resist its effects.[10–12] Antibiotics are also ineffective against biofilm growth as the molecules are unable to penetrate the extracellular polymeric substance (EPS) that encases biofilms (Fig. 1B).[13,14] The last strategy is the most invasive: the complete removal and replacement of the implanted device. Although device removal eliminates the infected material, infection may persist in surrounding tissue and be worsened by implantation-site stress. The procedure's severity varies by device, with simpler removals like intravascular catheters posing far less risk than complex devices such as synthetic heart valves due to differences in complexity and proximity to vital organs. Despite these drawbacks, healthcare professionals maintain that the benefits of device extraction outweigh the risks.

While bacterial infections pose a major threat to the integrity of implanted devices, thrombosis, occlusion, and embolism also threaten the functionality of implanted blood-contacting devices. Thrombosis, which is the aggregation of red blood cells, plasma proteins, and platelets through a signaling cascade,[15,16] can partially or completely block blood flow and become especially dangerous if they dislodge as emboli.[17,18] The emboli can potentially travel to vital organs and cause severe complications such as ischemic stroke. Nearly one million people in the United States have experienced venous thromboembolism, a number projected to rise by 82% by

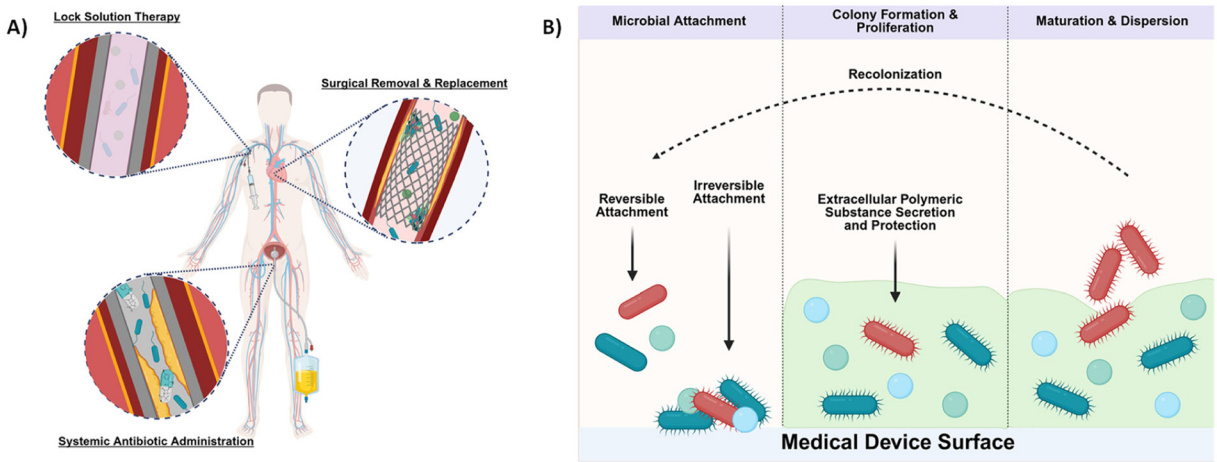

Fig. 1 (A) Examples of medical device infections and different methods to treat the infection, ranging from non-invasive to invasive. (B) Bacterial biofilm lifecycle. The bacteria begin an infection with reversible attachment to a device surface followed by irreversible attachment. Next, the bacteria begin to colonize and proliferate, secreting an extracellular polymeric substance (EPS) that protects the colony. Finally, the biofilm matures and disperses to begin the cycle again.

2050.[19] Typically, thrombosis is prevented by the systemic administration of anticoagulants, such as heparin, warfarin, or argatroban.[20–22] Unfortunately, systemic administration can have severe consequences such as excessive bleeding, bruising, and, in the case of heparin administration, thrombocytopenia.[23–25] Although the complications can become life-threatening, healthcare professionals still opt for clinical use of anticoagulants despite these consequences, as other strategies have not been as widely tested or accepted.

In response to the growing need for more biocompatible medical materials, research on novel combination strategies has been explored to address the shortcomings of traditional treatment methods; some of these technologies even have the potential to surpass current gold standards. As mentioned previously, bacterial infection and biofouling are some of the greatest factors in medical device failure and, therefore, need to be addressed in a non-invasive way and localized manner to prevent antibiotic resistance and delay device fouling. Biofouling can be broadly categorized into adherent foulants, such as bacteria, proteins, and platelets that firmly attach to material surfaces and initiate biofilm or thrombus formation, and non-adherent foulants, including planktonic bacteria, transient cells, debris, and microorganisms that can be more easily displaced but still contribute to early-stage contamination. One such strategy has been the development of slippery surfaces to prevent bacteria and other biofouling agents from adhering to biomaterial surfaces. Slippery surfaces typically employ a lubricant layer at the material-environment interface to physically prevent adhesion;[38] these surfaces, including slippery liquid-infused porous surfaces (SLIPS), smart slippery surfaces, and drug-releasing SLIPS have stemmed from the central concept of physical repulsion (Table 1).[38] Slippery liquid-infused porous surfaces were initially inspired by the *Nepenthes* pitcher plant, which capture prey using a permanently wetted, lubricant-stabilized surface that induces extreme slipperiness.[39] This biomimetic concept was first translated to synthetic materials through the infusion of lubricants into porous substrates,[26] creating stable liquid layers capable of repelling liquids and solids. More recently, SLIPS technologies have evolved beyond passive anti-fouling designs to incorporate biomedical functionality, including antimicrobial activity, drug release, and stimuli-responsive behavior tailored for medical device applications.[40]

Within biomedical contexts, these materials are particularly relevant for blood-contacting and indwelling devices, such as intravascular catheters and urinary catheters, where localized anti-fouling and antimicrobial performance is critical for prevention of infection, thrombosis, and device failure. Several reviews have previously summarized the development and performance of slippery surfaces for applications such as antibacterial coatings, anti-icing materials, and fouling-resistant interfaces.[41,42] However, these reviews have primarily focused on the materials and mechanisms of slippery behavior. In contrast, this review presents a more focused evaluation on the variations of slippery lubricant-infused surfaces, specifically reviewing traditional SLIPS materials compared to stimuli-responsive (smart) SLIPS, or bioactive SLIPS (materials that have a bioactive agent embedded within the lubricant), with an emphasis on comparatively assessing for their biocompatibility and relevance in medical applications.

2. Comparative analysis of slippery surfaces

Slippery surfaces have recently emerged as a formidable strategy for a novel approach towards more effective antimicrobial and anti-fouling materials. These materials are gaining prominence in biomedical applications not only for their ability to infuse into polymeric substrates but also for their remarkable anti-fouling and antibacterial benefits.[41,43] By integrating bioinspired materials with inherent slippery properties, biomedical devices can effectively resist the adhesion of biological substances, preventing fouling and microbial attachment.[27,44] This anti-fouling characteristic is particularly advantageous in applications such as vascular and urinary catheters, where bloodstream infections and biofilm formation pose a significant challenge. Furthermore, slippery surfaces can inhibit bacterial adhesion or blood cell aggregation, reducing the risk of infections and blood clots associated with medical implants or devices.[45–47] This dual functionality, combining reduced friction and resistance to fouling and bacterial colonization, enhances the overall performance, longevity, and safety of biomedical technologies, promising substantial improvements in patient outcomes and healthcare practices. However, as the slippery material is exposed to fouling environments for prolonged periods, there is an increased risk for the material to accumulate fouling agents on the surface due to lubricant depletion. With lubricant depletion and without means to remove accumulated foulants or prevent adhesion without contact, slippery materials become ineffective and a liability, exacerbating and prolonging infection and serious thrombosis. Therefore, much of the ongoing research on slippery materials looks to novel methods to retain the lubricant more effectively and address the prospect of preventing adhesion of fouling agents before making contact with the surface.

2.1. Prevention of adherent foulants

2.1.1. Slippery liquid-infused porous surfaces (SLIPS). The development of one type of slippery surface specifically mimicking the slippery nature of *Nepenthes* pitcher plants, has been credited to Wong *et al.*, with their slippery liquid-infused porous surface (SLIPS) material.[26] The plant exhibits a slippery nature due to wetting of the plant peristome (with ordered ridges that allow for significant lubricant retention)[39] that the researchers sought to mimic through artificial means. The SLIPS materials comprise a lubricant oil, often silicone or fluorinated oil, infused into a bulk porous substrate, creating a slippery lubricant layer at the surface level that can be replenished by the reservoir of lubricant within the bulk material.[26,48] The SLIPS allow various types of liquid media (*e.g.*, water) as well as solid materials (*e.g.*, bacteria, blood

Table 1 Examples of common lubricants and their substrates demonstrate the progression from passive anti-fouling to the incorporation of bioactive components. Detailed are the biological components that were repelled and/or cells they were compatible with and the limitations for translation

SLIPS type	Lubricant	Substrate	Biological component	Limitations	Ref.
Traditional	Perfluorotri-*n*-pentylamine (FC-70) Perfluoropolyether (Krytox® 100) Perfluoropolyether (Krytox® 103)	Polytetrafluoroethylene (PTFE) membrane	• Whole blood	Lubricant depletion	26
Traditional	Perfluorotri-*n*-pentylamine (FC-70) Perfluoropolyether (Krytox® 100) Perfluoropolyether (Krytox® 103)	PTFE membrane	• *P. aeruginosa* • *S. aureus* • *E. coli*	Lubricant depletion	27
Traditional	Perfluoropolyether (Krytox® 103)	Etched silicone wafers	• *S. aureus* • *E. coli*	Lubricant depletion	28
Traditional	Perfluoropolyether (Krytox® 103)	Zeolitic imidazolate framework-L-coated polyurethane	• Whole blood • *P. aeruginosa*	Lubricant depletion	29
Smart	Paraffin	Polystyrene	—	$T_{m\_paraffin}$ = 44°–46° (above physiological temperature)	30
Smart	MF02 (ferrofluid)	Etched Epoxy polymer	—	Ferrofluid may not be biocompatible; magnetic field necessary	31
Smart	Silicone oil Ionic liquid [VBIm][NTf_2]	Graphene oxide-coated surface	—	Conductive lubricant necessary	32
Smart	Soybean oil	Graphene oxide-coated surface	—	Material deformation space needed	33
Antimicrobial-agent releasing	Silicone oil	Nitric oxide (NO)-releasing silicone rubber	• Fibrinogen • Platelets • *P. aeruginosa* • *S. aureus* • NIH 3T3 mouse fibroblasts	Finite drug reservoir	34
Antimicrobial-agent releasing	*n*-Hexadecane nanoemulsion	Polytetrafluoroethylene (PTFE) membrane	• *P. aeruginosa*	Finite drug reservoir	35
Antimicrobial-agent releasing	Black seed oil	PDMS/polystyrene	• *S. aureus* • *E. coli*	Finite drug reservoir; no controlled release of drug	36
Antimicrobial-agent releasing	*n*-Hexadecane nanoemulsion	Expanded PTFE (ePTFE)	• Fibrinogen • *S. aureus* • *E. coli* • NIH 3T3 mouse fibroblasts • Human umbilical vein endothelial cells (HUVEC)	Finite drug reservoir	37

cells) to simply slide off the surface, typically due to a difference in surface tension between the lubricant medium and fouling liquid or agent.[26,38] The mechanism of slipping entails the wetting or full encapsulation of the foulant by the surface lubricant, thereby allowing the fouling agent to be physically removed from the surface.[26,38]

Recent research has demonstrated the antimicrobial and anti-fouling efficacy of artificially fabricated porous substrates, when combined with lubricant infusion, for SLIPS materials.[49–53] The dual functionality of the materials is induced by physical removal of fouling agents through slipping, such as bacteria, blood, and proteins, or a combination of slippery behavior and either contact killing or drug release for a bactericidal effect. Synthetically roughened or porous surfaces, such as surface etching, have been employed to fabricate uniform and ordered micro- and nanostructures on substrates for lubricant retention (Fig. 2A).[28,52] In this way, the porosity of the surface, an integral component in a SLIPS material, can be fine-tuned and controlled to induce a more effective retention of the lubricant oil, as demonstrated by prolonged efficacy over time.[28,29,49,52] With better retention of the lubricant, the surface is better able to repel fouling agents (Fig. 2B and C). Other means to artificially fabricate porous substrates by roughening smooth surfaces include nanoparticle deposition (*e.g.*, silica, zinc oxide, copper) on the surface (Fig. 2E).[51,54] While not as ordered as surface etching, nanoparticle depo-

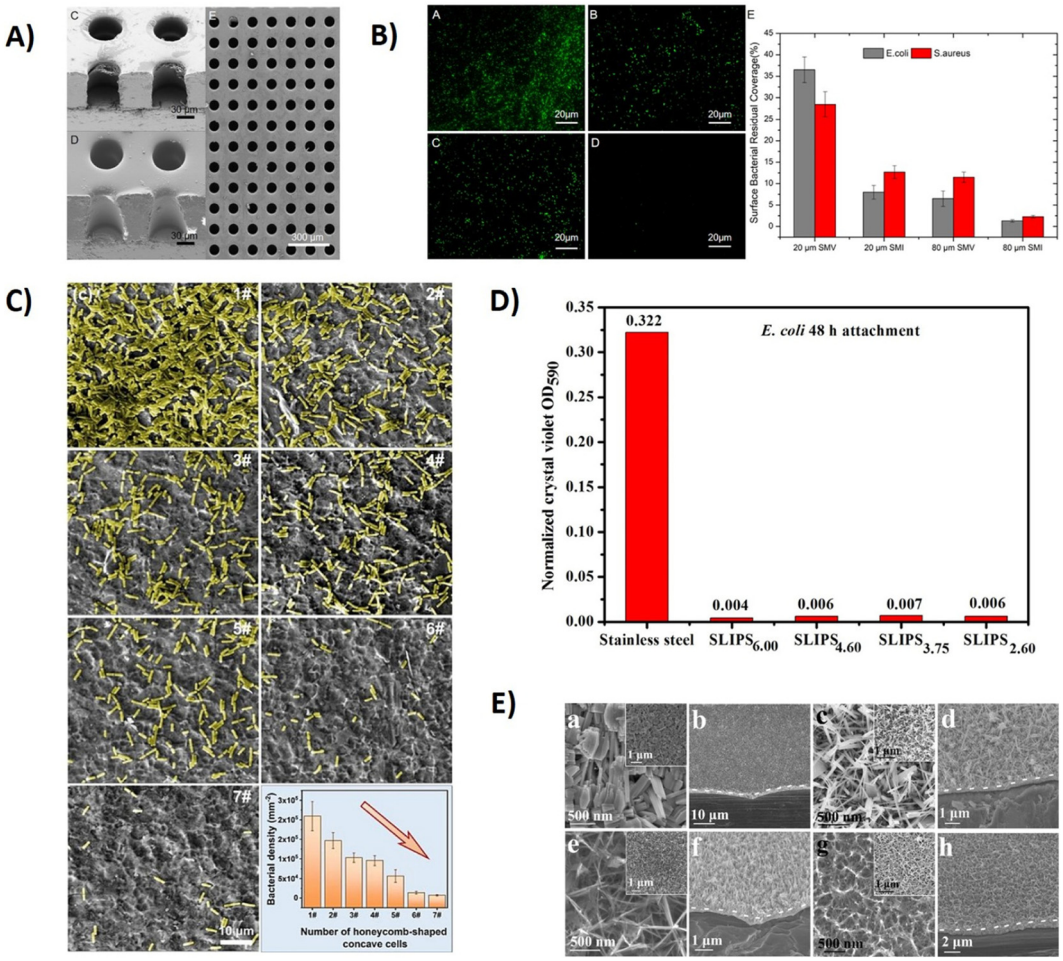

Fig. 2 (A) Scanning Electron Microscopy (SEM) of substrate etching on silicon wafers *via* ultraviolet (UV) exposure for uniform, inclined cavities. The inclined cavities' shape is able to retain lubricant more effectively in part due to the greater volume compared to the vertical cavities. (B) Fluorescent images of *E. coli* biofilms and bacterial coverage on the inclined pores surface after immersion for 2 days in dynamic conditions. Reprinted from *Colloids and Surfaces B: Biointerfaces*, 202, Guangyi Cai, *et al.*, Slippery liquid-infused porous surfaces with inclined microstructures to enhance durable anti-biofouling performances, 111667, Copyright 2021, with permission from Elsevier.[28] (C) SEM images of the adhesion of *Pseudoalteromonas* on the titanium alloy SLIPS material at different honeycomb-shaped concave pores. The density of the bacteria decreased as the number of concave cells increased, probably due to the increased lubricant retained. Reprinted from *Chemical Engineering Journal*, 478, Zeping Zhang, *et al.*, Improving anti-fouling functions of titanium alloys by robust slippery liquid-infused porous surfaces with tailored multiscale structures, 147342, Copyright 2023, with permission from Elsevier.[77] (D) Crystal violet staining of *E. coli* on the tungsten oxide-SLIPS material after 48 h incubation. (E) SEM images of tungsten oxide nanostructures after deposition. Adapted in part with permission from ref. 51. Copyright 2020 American Chemical Society.[51]

sition can still produce uniform but random aggregates that act as the porous substrate for lubricants.[51] In the same way as other artificially roughened surfaces for porous substrates, the nanoparticle aggregates may better retain the lubricant infused into the substrate to enhance the available lubricant reservoir and demonstrate excellent contact angle hysteresis and sliding angle against water and whole blood, as well as prevent bacterial adhesion and proliferation (Fig. 2D).[51]

Although these slippery materials demonstrate effective physical prevention of bacterial adherence and whole blood fouling, no active bactericidal or antithrombotic effect is especially apparent in traditional SLIPS materials, even those with artificially porous substrates. The anti-fouling and antibacterial performance comes purely from the physical repulsion of the foulants alone.[28,50] This may limit the efficacy of the material in biomedical applications or environments that require planktonic prevention and may not be as desirable.

While some surface roughened techniques do not provide means for bactericidal activity, others, such as the fabrication of metal organic frameworks (MOFs) on a smooth surface to form nanostructures,[29,49] acts as an artificially porous surface that can be oriented to form nanostructures, such as dagger-like or rod-like shapes (Fig. 3A),[29,49] that facilitate the lubricant infusion and induce bacterial contact killing upon lubricant loss and bacterial adhesion (Fig. 3B) to the surface and repel whole blood.[29,49] These MOF surfaces may physically puncture bacterial membranes, but other methods to induce contact killing in the presence of lubricant depletion have also been investigated, such as functionalizing a porous surface with a bactericidal quaternary ammonium group (QAC) silane.[53,55] Similarly to the MOF-SLIPS surfaces, the QAC-silane SLIPS demonstrated significantly reduced bacterial adhesion against *S. aureus* and *E. coli* and elicited no hemolytic effects when tested against whole blood.[53] Although these contact killing methods address the lubricant depletion problem, the problem of surface fouling still remains. If the lubricant is depleted and no longer functional, there is no strategy to remove the dead foulants. As a result, traditional SLIPS are most suitable for short-term or low-fouling biomedical applications where passive anti-fouling alone, rather than active antimicrobial or antithrombotic functionality, is sufficient.

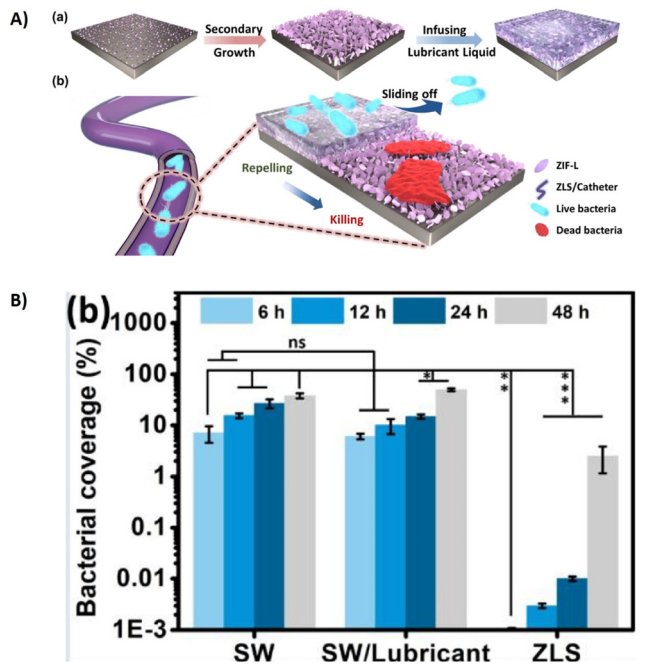

Fig. 3 (A) Metal organic framework deposited on a flat surface and infused with lubricant. The zeolitic imidazolate framework-L (ZIF-L) was deposited on a surface to form the dagger-like structures. The lubricant was then infused into the roughened surface (ZLS) to induce a slippery surface. (B) Bacterial coverage of *P. aeruginosa* after 6, 12, 24, and 48 h on a silicone wafer (SW), a silicone wafer with lubricant coating (SW/lubricant), and the lubricant-infused MOF surface (ZLS). Reprinted from *Applied Materials Today*, 27, Lingwan Hao, *et al.*, Metal–organic framework (MOF)-based slippery liquid-infused porous surface (SLIPS) for purely physical antibacterial applications, 101430, Copyright 2022, with permission from Elsevier.[29]

2.1.2. Smart slippery liquid-infused porous surfaces (smart SLIPS). The fundamental concept behind the repelling mechanism of smart SLIPS is the same as that of SLIPS: the infusion of a lubricant into a porous substrate to prevent fouling and adhesion. However, unlike traditional SLIPS strategies, which are considered passive for anti-fouling and antibacterial activity, smart SLIPS have a responsive component that modulates its efficacy. The "smart" functionality of these slippery materials is activated by external stimuli, such as heat, light, or magnetic fields, to induce responsive slippery behavior with tunable anti-fouling activity.[31,56–58] Many smart SLIPS materials also incorporate anisotropic or responsive substrates; in other words, the directionality of the features on the substrate or material deformation is used to direct the direction of flow of the foulant medium.[30,31] With the capability of controlling the slippery behavior of a material, smart SLIPS materials have the potential for on-demand slipping behavior and antibacterial effects.

Smart SLIPS materials typically incorporate a responsive lubricant, such as thermo-responsive, ferrofluidic, or photo-responsive fluids, that can behave as anti-foulants in response to applied stimuli. Often, the surfaces that smart lubricants infuse into are artificially roughened as well; however, recent research has used ordered, directional etching *via* laser ablation or freeze drying methods to control the direction of fluid flow (Fig. 4).[31,32] In this way, the chosen stimuli are able to induce a sliding or pinning motion of the foulant liquid depending on the state of activation. Because the materials can function and respond to stimuli, the fluid can move against gravity or remain pinned to the surface even when tilted (Fig. 4).[30,31] While smart SLIPS may seem advantageous for their tunability, in practice, even with ordered, directional surface etching, materials that use these responsive lubricants in combination with surface etching typically perform worse than traditional SLIPS materials. Where traditional SLIPS materials demonstrate low sliding angles, low contact angle hysteresis, and have been proven to reduce bacterial and blood adhesion,[26,38,48,52,53,59] smart SLIPS materials are barely able

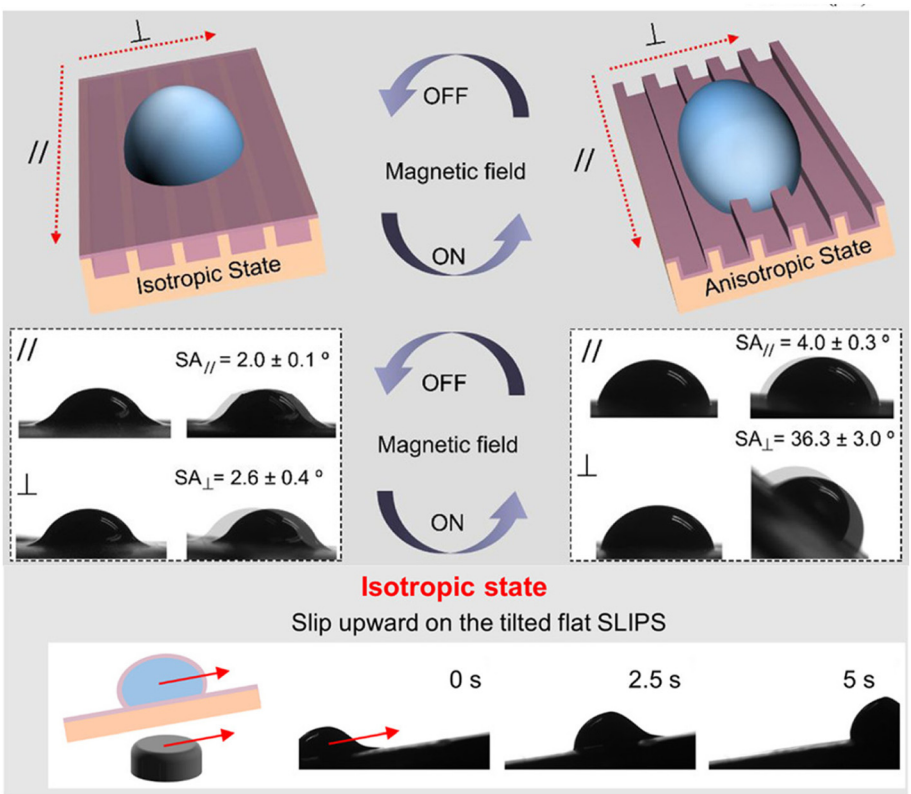

Fig. 4 A magnetically stimulated, anisotropic slippery surface that exhibits different slippery behaviors with a magnetic field present or absent. The sliding angle (SA) of a liquid droplet was characterized parallel (||) to and perpendicular (⊥) to the surface etching. It was observed that the SA of the material could be controlled to prevent sliding in the perpendicular direction when the magnetic field was on. Adapted in part with permission from ref. 31. Copyright 2020 American Chemical Society.[31]

to induce a sliding effect of foulants at ~40°.[30,31] The limited efficacy of smart SLIPS reported to date may be attributed to larger surface features that promote foulant adhesion or to higher surface tensions between the responsive lubricant and the fouling agent.

Some smart SLIPS leverage the substrate's responsive behavior to stimuli, such as moisture, to mechanically deform the material and repel foulants.[33] Han *et al.* is one of the few groups to have combined SLIPS with responsive substrates in this manner.[33] The physical deformation of the responsive substrate, in combination with lubricant infusion, could then physically contract and force solid and liquid foulants to slide off of the surface. This method has been proven to repel several complex, though not biologically relevant, liquids, such as plum juice, beer, and milk, as well as small organisms.[33] The slippery ability of the lubricant infusion prevents liquids from adhering to the substrate surface due to the difference in surface tension, while the material deformation aids in true removal from the surface.[33] However, no work has been conducted to assess the efficacy of these materials against bacterial infection or whole blood exposure *in vitro* or *in vivo*, thus making it difficult to conclude whether this material would be applicable for biomedical devices.

A more medically relevant work by Wang *et al.* utilizes thermo-responsive paraffin as the slippery medium.[30] Paraffin is commercially available in solid wax form and is typically used for non-medical purposes, such as candle-making. However, in this work, the paraffin was imbued into a directionally porous substrate to fill gaps left by the pores. At room temperature, the paraffin remains solidified and does not provide any bioactive antimicrobial or anti-fouling activity. In essence, the surface may attract bacteria and biofouling debris to adhere without mechanisms to remove them, thus promoting infection and thrombosis. When exposed to elevated temperatures near physiological levels, the paraffin underwent a phase change, becoming more liquid-like.[30] This liquid state of the paraffin acts like a slippery liquid-infused surface, allowing for fouling agents to slide off the surface.

Taken together, smart SLIPS materials showcase how dynamic, stimuli-responsive design can elevate traditional slippery interfaces into highly adaptive, multifunctional systems capable of responding to complex biomedical environments. By incorporating triggers such as pH, temperature, enzymes, light, or mechanical stress, smart SLIPS can autonomously adjust lubricant distribution, modulate surface chemistry, or release therapeutics only when and where needed, thereby significantly enhancing precision and reducing off-target effects. Despite their adaptive design, the current performance limitations of smart SLIPS restrict their immediate translational use in biomedical devices that require consistently low sliding

angles, high durability, and validated performance under physiological flow conditions. While challenges remain in balancing responsiveness with stability and ensuring biocompatibility of the triggering mechanisms, ongoing innovations continue to expand the capabilities of these materials. Ultimately, smart SLIPS are adaptive, interactive, and tailored to meet the dynamic conditions encountered in real-world biomedical applications.

2.2. Prevention of non-adherent foulants

2.2.1. Antimicrobial agent-releasing slippery liquid-infused porous surfaces (SLIPS). While roughened surfaces infused with a bioinert lubricant oil may help to prevent adherent foulants from adhering and proliferating with lubricant depletion, they would be useless against planktonic or non-adherent foulants because no bioactive antimicrobial agent is loaded into the lubricant or substrate to diffuse into the surrounding environment from the matrix. Direct contact with the lubricant is necessary to be slippery and anti-fouling. Therefore, the research developed into antimicrobial agent-loaded SLIPS materials to bridge the gap between bioinert and bioactive slippery interfaces. Because traditional SLIPS typically use oil as the lubricant, the drug or small molecule must be able to diffuse through the lubricant phase to achieve any applicable effect. While some drugs may be oil-soluble, such as the broad-spectrum antimicrobial agent triclosan, the amount of drug loaded into the oil phase would be difficult to control.[60] The solubility limit of the drug molecule in the lubricant phase would hinder the amount of usable antimicrobial agent. Additionally, the stability of the antimicrobial agent may also be affected as a solubilized agent rather than an isolated drug.[60] Instead of loading the drug directly into lubricant oil, it is loaded into the porous substrate to incorporate a larger drug reservoir for controlled release.[59,60] Using this strategy, the loaded substrate does not compromise slippery behavior and exhibits excellent anti-fouling abilities with significantly lower sliding angles and contact angle hysteresis, as well as exceptional antimicrobial efficacy with significant reductions in fungal[60] and bacterial[59,60] adhesion (Fig. 5A). Other antimicrobial agents, such as the gasotransmitter nitric oxide (NO), have also been incorporated into polymer substrates, such as silicone rubber[34,61–63] or gel platforms,[64,65] and infused with a lubricant oil to elicit a dual antimicrobial and anti-fouling effect. Because NO is a small gaseous free radical, it can readily permeate through diverse oils and substrates,[66] offering a distinct advantage over bulkier antimicrobial or anticoagulant drug molecules. Like the triclosan-loaded substrate, the NO-releasing material releases the antimicrobial agent as the biocidal component while the lubricant layer mainly prevents the adhesion of the foulants, again demonstrating (1) excellent retention of the slippery behavior, (2) both antimicrobial and anti-fouling efficacy against common pathogens, and (3) applicability under complex fluid flow. In this way, these drug-loaded SLIPS materials improve upon existing technology to address the need for methods to prevent planktonic foulants from attaching to surfaces.

Similarly, a recent development of slippery nanoemulsion-infused porous surfaces (SNIPS) has been derived from SLIPS (Fig. 6).[35] Unlike the homogenous oil lubricant of SLIPS, SNIPS incorporates a water-in-oil (w/o) nanoemulsion as its lubricant media (Fig. 5B), where a nanoemulsion is a mixture of more than one immiscible fluid through mechanical shear.[67] The capability to load a water-soluble drug into the w/o nanoemulsion enables the infused substrate to have an

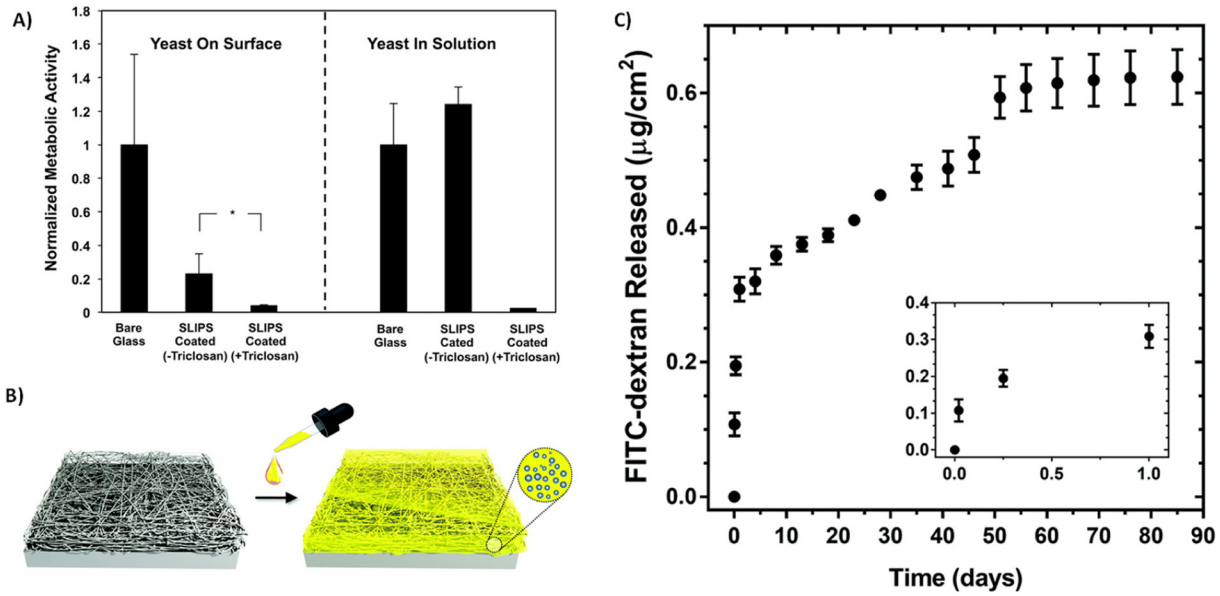

Fig. 5 (A) Metabolic activity of triclosan-loaded SLIPS materials where the triclosan is loaded into the substrate. Adapted in part with permission from ref. 60. Copyright 2016 John Wiley and Sons.[60] (B) Schematic of a slippery nanoemulsion-infused porous surface (SNIPS). (C) Release of FITC-tagged dextran from the SNIPS over 80 days. Reproduced from ref. 35 with permission from the Royal Society of Chemistry.[35]

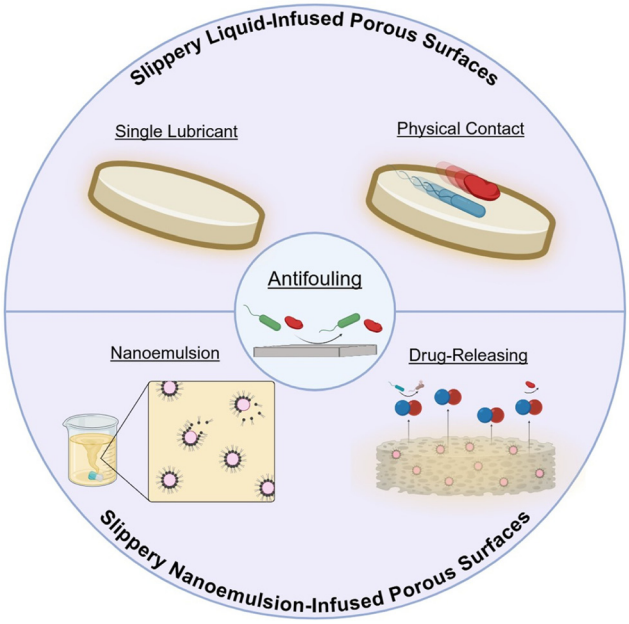

Fig. 6 Comparison of SLIPS *versus* SNIPS. Slippery liquid-infused porous surfaces uses a single lubricant and requires physical contact for anti-fouling efficacy. Slippery nanoemulsion-infused porous surfaces, on the other hand, employs a nanoemulsion that can be loaded with a water-soluble therapeutic or drug for enhanced efficacy in combination with slippery behavior.

aqueous bioactive component to its antimicrobial activities, overcoming the need for an oil-soluble agent.[35] Recent reports have incorporated an aliphatic lubricant-based nanoemulsion into a porous polytetrafluoroethylene (PTFE) membrane[35] and expanded PTFE (ePTFE),[37] exhibiting the nanoemulsion's ability to easily swell into porous membranes. The aqueous droplet phase of the nanoemulsion enables hydrophilic drug incorporation into these highly hydrophobic substrates that would otherwise not be possible without complex fluorochemistry.[68,69] As a recent modification to the slippery surface technique, preliminary research has been conducted with SNIPS surfaces to demonstrate its anti-fouling efficacy against complex fluids like porcine whole blood and human urine[35] and antibacterial efficacy against Gram-positive *S. aureus* and Gram-negative *P. aeruginosa*[35] and *E. coli*.[37] Drug-releasing capability was demonstrated in short-term applications with 24 h release of NO[37] at therapeutic concentrations ($0.5–4 \times 10^{-10}$ mol min^{-1} cm^{-2})[70] and a longer-term application through monitoring of a FITC-tagged water-soluble molecule over 80 days (Fig. 5C) and found to have a slow, controlled release over that time period.[35] Although the preliminary SNIPS material was a proof-of-concept, its anti-fouling ability performed well and was comparable to its SLIPS parent material, able to repel the complex liquids in under 2 seconds.[35] Also comparable to traditional SLIPS materials is the SNIPS' ability to prevent bacterial adhesion with significant reduction of *S. aureus*, *P. aeruginosa*, and *E. coli* adhesion to the nanoemulsion-infused surface. While this SNIPS material does not induce contact killing as artificially roughened surfaces with lubricant infusion might, its ability to load water-soluble drugs into the composition of an otherwise hydrophobic substrate is advantageous since aqueous antimicrobial agents can be loaded for bioactive release and activity.

In other cases, the oil itself may exhibit slippery behavior and antibacterial properties. Several natural or benign oils used as lubricants in SLIPS materials, like black seed oil and olive oil, contain bioactive constituents (*e.g.*, linoleic acid, oleic acid, thymoquinone, and long-chain hydrocarbons)[71] that inherently disrupt bacterial viability. These components often behave as amphiphilic fatty acids or surfactant-like molecules that can insert into the bacterial lipid bilayer. Their insertion increases membrane permeability, disrupts phospholipid packing, and destabilizes membrane integrity, ultimately predisposing the cell wall to rupture or lyse.[36,72–74]

Although these systems do not fall under "drug-releasing" SLIPS in the traditional engineered sense, the fundamental mechanism of SLIPS, where lubricants remain surface-bound through capillarity yet slowly deplete under shear, diffusion, or environmental exposure, effectively results in passive release of these bioactive compounds. As the lubricant gradually leaches into the surrounding medium, its antibacterial constituents diffuse outward, creating a localized biocidal environment. This behavior mimics the therapeutic release profiles observed in intentionally drug-loaded SLIPS, but here the antimicrobial effect arises solely from the chemical nature of the lubricant rather than an added pharmaceutical agent. Consequently, intrinsically active oils offer a simplified design route for antibacterial SLIPS coatings by combining surface slipperiness, fouling resistance, and passive antimicrobial action within a single material component.

A crucial component of indwelling medical devices, especially blood-contacting devices, is the complex nature of the *in vivo* environment, including blood cells, plasma proteins, and dynamic conditions. Of the antimicrobial agent-loaded slippery substrates discussed, only the NO-releasing substrates actively prevent thrombosis through the inactivation of platelets.[75] The other bioactive agents mainly target pathogens and do not specifically address thrombotic events, such as red blood cell and platelet aggregation and protein adsorption. Even NO-releasing substrates, which have shown to increase fibrinogen adsorption, struggle to prevent protein fouling.[76] Therefore, the anti-fouling ability of slippery substrates is especially vital for enhancing the overall hemocompatibility of these materials. Previously reported SLIPS substrates have demonstrated significant reduction of platelet aggregation and protein adsorption,[34,62] pointing towards the enhanced anti-fouling efficacy of these slippery surfaces. The low surface tension from the lubricants prevents highly adherent foulants from sticking to the surface and improving the material's biocompatibility.

Overall, antimicrobial agent-releasing SLIPS represent a versatile and powerful strategy for combating biofouling by coupling the passive repellency of liquid-infused interfaces with the

targeted activity of therapeutic payloads. These systems are particularly promising for biomedical devices exposed to complex biological environments, as they simultaneously address adherent fouling on device surfaces and non-adherent planktonic pathogens in the surrounding tissue or fluid. By leveraging diverse release mechanisms, including diffusion-driven elution, shear-triggered depletion, lubricant-mediated solubilization, and stimuli-responsive activation, these systems can deliver antimicrobial agents in a controlled and sustained manner while maintaining the hallmark ultra-slippery, anti-adhesive behavior of SLIPS. Importantly, the ability to integrate small-molecule agents, metal ions, natural bioactive compounds, and biologics enables broad customization across diverse biomedical environments. Although optimizing release kinetics, minimizing lubricant loss, and preventing the development of resistance remain ongoing challenges, recent advances demonstrate that SLIPS can serve not only as passive anti-fouling surfaces but also as dynamic, therapeutically active coatings. Together, these innovations position agent-releasing SLIPS as a promising class of multifunctional materials capable of addressing persistent infection risks across a wide range of medical device applications.

2.3. Current limitations and the biomedical implications

While slippery surfaces have been extensively reported, their translation to biomedical applications imposes additional constraints, including long-term biocompatibility, lubricant retention under physiological shear, and robust adhesion to medical-grade polymer substrates. Slippery liquid-infused porous surfaces, particularly those with artificially porous substrates, have repeatedly been shown to exhibit low contact-angle hysteresis, inhibit bacterial adhesion and infection, and prevent whole-blood adhesion.[26,47,51,77] In biomedicine, SLIPS find utility in biocompatible coatings for medical implants, reducing biofouling and extending their lifespan. They enhance drug-delivery systems by ensuring efficient release and can serve as antibacterial surfaces that inhibit biofilm formation and contribute to infection prevention. However, the main challenge of SLIPS materials has been the depletion of surface lubricant and substrate reservoir and the fact that there is no efficacy, antibacterial or anti-fouling, without contact on the surfaces.[38,41,43] The SLIPS materials rely on a lubricant layer to prevent fouling and bacterial adhesion; however, as the lubricant degrades, the surface may lose effectiveness, increasing susceptibility to fouling and reducing overall performance. Any modifications made to artificially induce bactericidal activity or antithrombotic efficacy after the lubricant is lost lack a strategy to remove dead bacteria, debris, or fouling agent accumulation thereafter. The defunct surfaces would become a prime site for infection and thrombosis, negating the intended effect.

Taking it a step further, smart SLIPS incorporate responsive features, allowing adaptation to environmental stimuli. These include responsive lubricants, self-healing properties, and stimulus-triggered drug release, providing controlled and targeted drug delivery.[31–33,56,58] Adaptive anti-fouling capabilities and integration into diagnostic tools make smart SLIPS versatile for various biomedical applications, such as drug delivery or implant coatings. Although the responsive behavior of the slippery surface holds much promise for the tunability of the material, the reports of smart SLIPS surfaces, their sliding angle, contact angle hysteresis, stability, and lack of evidence agent biological media,[31,33,56] are not as comparable to traditional SLIPS, making them less suitable for immediate use in clinical applications.

Of the aforementioned strategies, the antimicrobial agent-releasing SLIPS materials hold the most promise compared to traditional SLIPS or smart SLIPS in that the antimicrobial agent-releasing SLIPS materials have the potential to impede both adherent and non-adherent foulants.[34,35,59,60,62] Not only can antimicrobial agent-releasing SLIPS materials be used in the same applications as traditional or smart SLIPS, but they also address the planktonic foulants in biological environments. The slippery nature of these materials still requires some level of contact to primarily prevent foulant adhesion, but the bioactive component to the substrate or lubricant itself provides an enhanced edge over both traditional and smart SLIPS.

Beyond lubricant depletion and sliding performance, the translation of SLIPS technologies to biomedical applications introduces additional constraints. These include the long-term biocompatibility of lubricants and infused agents, robust adhesion of SLIPS coatings to medical-grade polymer substrates, and resistance to delamination under dynamic physiological conditions. Ensuring that the slippery coating remains viable for prolonged periods will enhance the biocompatibility and patency of the material for various applications like long-term catheterization or vascular grafts. For antimicrobial agent-releasing SLIPS, matching release kinetics to clinically relevant therapeutic windows remains a critical challenge, as premature depletion or insufficient dosing may limit efficacy. In this scenario, the passive anti-fouling surface must compensate for the loss of bioactivity. Addressing these biomedical-specific requirements will be essential for clinical adoption.

3. Conclusion

While many patients admitted to hospitals may only experience some low-level or non-invasive medical treatment, others are subjected to more complicated practices and invasive treatments, such as surgeries and medical device implantation to support normal bodily function. However, the risks and complications associated with these invasive strategies, like severe bacterial infections, biofilm formation, thrombosis, and biofouling, would not only compromise the host immune response, homeostasis, and bodily repair, it would also compromise any indwelling devices, like intravascular catheters or vascular stents, meant to aid in the treatment or healing process. Bacterial infections associated with implanted medical devices, arising from either the patient's natural skin microbiome or contamination at the time of implantation,

pose a major challenge for the devices, as they can elicit adverse immune responses and progress to more severe infections and biofilm formation. The primary current strategy to combat infections is systemic administration of antibiotics; however, antibiotics are ineffective against biofilms because they cannot penetrate the extracellular polymeric substance. Thrombosis and blood clots associated with blood-contacting devices also pose a threat to the functionality of the device as it can cause occlusion. Again, the main current strategy here is the systemic administration of anticoagulants, which have adverse side effects that include excessive bleeding, bruising, or thrombocytopenia. Both bacterial infections and thrombosis have an aspect of biofouling that must be mitigated to prevent further complications.

The critical challenges associated with medical device complications, particularly infections and fouling, and the subsequent impact on patient health and treatment costs are a significant battle in biomedical device design. The slippery surfaces, including SLIPS and smart SLIPS, demonstrate substantial potential in biomedical applications by minimizing friction, resisting fouling, and inhibiting bacterial adhesion. However, concerns related to lubricant depletion and the efficacy of responsive features in smart SLIPS need further exploration. The most promising approach appears to be antimicrobial agent-releasing SLIPS materials, which not only address adherent foulants but also combat non-adherent ones, providing a comprehensive solution for medical device applications. Looking ahead, key breakthroughs in SLIPS research are expected to focus on improving long-term lubricant retention, ensuring lubricant and coating biocompatibility, and integrating multifunctional therapeutic release without compromising surface stability. These may be achieved through a combination of roughened surfaces infused with inherently antimicrobial lubricants. Advances in scalable manufacturing, robust coating adhesion under physiological shear, and validation in clinically relevant models will be essential for translation. In particular, antimicrobial agent-releasing SLIPS are promising for impact in blood-contacting and indwelling medical devices, where combined anti-fouling and bioactive performance is critically needed.

Author contributions

Grace H. Nguyen: conceptualization, investigation, visualization, writing – original draft, writing – review & editing. Elizabeth J. Brisbois: project administration, supervision, funding acquisition, writing – review & editing.

Conflicts of interest

The authors declare the following competing financial interest (s): Elizabeth J. Brisbois is a cofounder and maintains a financial interest in a startup company investigating nitric oxide as a biomedical therapeutic for medical devices.

Data availability

This manuscript is a review of recent literature. All data that is presented can be found in the original research articles that are cited.

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