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Review

Antibacterial Coatings: Challenges, Perspectives, and Opportunities

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Antibacterial coatings are rapidly emerging as a primary component of the global mitigation strategy of bacterial pathogens. Thanks to recent concurrent advances in materials science and biotechnology methodologies, and a growing understanding of environmental microbiology, an extensive variety of options are now available to design surfaces with antibacterial properties. However, progress towards a more widespread use in clinical settings crucially depends on addressing the key outstanding issues. We review release-based antibacterial coatings and focus on the challenges and opportunities presented by the latest generation of these materials. In particular, we highlight recent approaches aimed at controlling the release of antibacterial agents, imparting multi-functionality, and enhancing long-term stability.

Trends

Coatings releasing antibacterial agents have shown great potential to reduce nosocomial infections.

The development of controlled release strategies is necessary to optimize therapeutic effects.

Next-generation coatings should be multifunctional and integrate multiple antibacterial effects.

Standardized assessment of both stability and antibacterial properties still need to be addressed, especially for long-term applications.

Antibacterial Surfaces in Health Applications

Advances in Biomedical Engineering Prompted by the Development of New Materials

Recent advances in materials science have brought about high-performance, multifunctional materials with bioactive properties [1]. Materials bulk properties determine the general mechanical behavior, while bioactivity is linked to surface properties. The main driving force for developing biocompatible coatings is the increased performance of functionalized surfaces that cannot be achieved by bulk materials. Thin films can simultaneously satisfy multiple requirements with respect to stability in biological environments, for example, mechanical (hardness, Young's modulus, stress), tribological (wear resistance, friction, adhesion), chemical (corrosion resistance), and others.

Nosocomial Infections and the Role of Surfaces

So-called nosocomial (hospital-acquired) infections result from hospital or healthcare service unit treatment, but are secondary to the original condition of the patient [2]. Such infections are considered a major health challenge in healthcare units worldwide. The prevalence rate of nosocomial infections, which are primarily caused by bacterial colonization of a broad range of biomedical surfaces, generally ranges from 4% to 10% (reaching up to 30% in intensive care units) in western-industrialized countries, making them the sixth leading cause of death [3–6]. The proportion is typically higher (>15%) in the developing world [7]. It is fortunate that the operating room is a sterile environment because it is filled with the largest number of potentially-infectious objects: instruments, the back table, the surgical table, monitoring/anesthesia equipment, and drapes. Although ventilation follows strict requirements during the design of an operating room, it is also considered as a major cause of bacterial contamination at the surgical area [8]. Consequences are catastrophic, especially in high-risk operations (open heart, prosthesis implantation, etc.). In

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2011, an estimated 722 000 nosocomial infections occurred in the USA, resulting in nearly 75 000 deaths [9]. Estimates of the annual cost range from $4.5 billion to over $11 billion.

It is now widely accepted that bacteria survive by attaching to solid substrates, in sessile structured communities called biofilms, where they can persist for extended periods, acting as a reservoir of pathogens and multiplying their pathways of transmission [10,11]. Bacteria in biofilms are drastically more resistant to antibiotics and external forces and can withstand host immune responses [12]. In addition, most nosocomial infections can be attributed to Gram-negative bacterial pathogens, for which there is a dwindling supply of antibiotics [13]. There is also increasing epidemiological evidence that, in addition to indwelling devices and implants, surfaces in the near-patient environment play a major role in the spread of nosocomial infections [9,14,15].

Importance of Antibacterial Coatings

Preventing the bacterial colonization of biomedical surfaces is the key to limiting the spread of infections. Nowadays, the bulk properties (e.g., mechanical) of materials in health applications have been more or less fully optimized. On the other hand, thin films can impart desired surface functions without affecting bulk mechanical properties. Antibacterial coatings have become a very active field of research, strongly stimulated by the increasing urgency of identifying alternatives to the traditional administration of antibiotics.

There are three major strategies for designing antibacterial coatings: antibacterial agent release, contact-killing, and anti-adhesion/bacteria-repelling (Box 1). The last two non-release approaches will be only briefly described in this review; interested readers are directed to other

Box 1. Main Approaches to Antibacterial Surfaces

Antibacterial Agent Release

Release-based coatings exert their antibacterial activity by leaching loaded antibacterial compounds over time, which allows killing of both adhered and adjacent planktonic bacteria. The release of incorporated antibacterial agents is achieved by diffusion into the aqueous medium, erosion/degradation, or hydrolysis of covalent bonds [31]. Compared with traditional antibiotic delivery methods, direct elution from the material surface offers the possibility to deliver a high antibacterial agent concentration locally, without exceeding systemic toxicity or ecotoxicity limits. It provides antibacterial activity only where needed, thus minimizing the development of resistance and avoiding potentially harmful systemic repercussions. However, because coatings have inherently limited reservoirs of antibacterial agents, their action is ultimately only temporary.

Contact-Killing

Contact-killing coatings have been developed to circumvent the reservoir exhaustion issue of release-based materials [115]. In this approach, antimicrobial compounds are covalently anchored to the material surface by flexible, hydrophobic polymeric chains. Adhered bacteria are believed to be killed due to disruption of their cell membrane by the attached compounds, reaching across the microbial envelope thanks to the long tethering chains [26]. Because the main mechanisms of action are based on membrane interactions, such as physical lysing or charge disruption, the most effective compounds for contact-killing coatings have been either cationic compounds (QACs, chitosan, AMPs, etc.) or enzymes [17].

Anti-Adhesion/Bacteria-Repelling

Anti-adhesion coatings seek to prevent the earliest step of biofilm formation using non-cytotoxic mechanisms. Bacterial adhesion at biomaterial surfaces is generally described using a two-stage model: an initial, rapid and reversible stage (stage I), mediated by non-specific physicochemical interactions, followed by a secondary 'locking' stage (stage II) involving, among others, species-specific bacterial adhesion proteins [116]. Surface immobilization of molecules that can resist protein adsorption, such as PEG and zwitterion, have demonstrated great anti-adhesion properties *in vitro* and, despite stability issues, are generally regarded as the standard approach for anti-adhesion coatings. However, the use of physical surface modifications (especially surface topography) as non-specific methods to modulate bacterial adhesion is most likely more complex than previously thought [103,117,118].

reviews that have documented these approaches in detail [16–18]. By contrast, the present review offers a critical overview of research on antibacterial agent release systems and will then discuss some recent and innovative strategies.

Relevance of Release-Based Antibacterial Coatings

The first generation of release-based coatings mainly consisted of devices impregnated with antibiotics or silver compounds [19]. An in-depth analysis of the body of literature from the past decade offers contradictory findings on the performance of this first generation of coatings. On the one hand, their introduction was associated with a significant decline in nosocomial infections [20–22]. On the other, several clinical trials revealed only limited success or reported complications [23,24]. Frequent issues linked with release-based coatings are limited reservoirs/lack of long-term properties, cytotoxicity, inflammatory responses, and increase in resistance of bacterial strains [12,25]. These concerns have spurred recent major advances in antibacterial coatings towards non-release approaches [26].

Recent Developments in Antibacterial Strategies

New evidence has emerged that could bring release-based coatings back to the forefront of the fight against nosocomial infections. For example, using a paradigm that originated from cancer treatment, researchers have identified hundreds of drugs that could be deployed cyclically in a sustainable process such that the same antibiotics could be used continuously without the risk of developing bacterial resistance [27]. This approach, termed collateral sensitivity cycling, takes advantage of the hypersensitivity to other drugs of multidrug-resistant pathogens. It could be particularly useful for Gram-negative bacterial pathogens, where multidrug resistance has increased rapidly. Similarly, newly discovered antibiotics, such as teixobactin, are likely to completely avoid the development of resistance. This was achieved by targeting less-mutable components of the bacteria (lipid precursors of cell wall components) rather than relatively mutable proteins [28].

In addition, viable alternatives to biocidal antibacterial agents are being widely investigated. Bacteria secrete and detect signaling molecules (autoinducers), enabling cell to cell communication (quorum-sensing, QS) and the regulation of several bacterial processes, including gene expression, virulence factor production, and biofilm formation [29]. Consequently, molecules that target and disrupt QS have garnered increasing interest as releasable antibacterial agents. Gram-positive bacteria typically use peptides for intercellular communication, while this role is fulfilled by acylhomoserine lactones (AHL) in Gram-negative bacteria [29]. By inducing less evolutionary stress on bacteria than biocidal compounds, QS inhibitors are less likely to induce the development of resistance. Another key target for bacterial signaling disruption is a small messenger molecule, *bis*-(3′-5′)-cyclic dimeric guanosine monophosphate (c-di-GMP), known as a central regulator of biofilm formation and dispersal in a wide variety of bacteria by controlling the switch between motile planktonic and sedentary, biofilm-forming phenotypes [30]. Altering intracellular c-di-GMP concentrations, either through c-di-GMP analogs or inhibitors, could emerge as a new pathway to reduce biofilm formation and biofilm-related infections.

There are still major issues related to anti-adhesion and contact-killing surfaces. Surfaces become rapidly contaminated with materials that attach non-specifically or are buried under a layer of dead cells, resulting in their deactivation [25,31,32]. In addition, because their antibacterial action requires very close proximity with bacteria, both approaches require defect-free surfaces, thereby making large-scale production and subsequent handling even more challenging.

Key Challenges

Antibacterial agent release and antibacterial coatings in general should not be viewed as a panacea or universally effective strategy. Rather, they should be considered as part of a concerted effort to control known risk factors of nosocomial infections. Even so, several key challenges must be

overcome for release-based coatings to become a truly useful tool in the fight against pathogens. We have identified these to be: (i) controlled release, (ii) multi-functionality, and (iii) long-term stability.

Release-Based Coatings

Over the past decades a broad range of antibacterial compounds have been developed for release-based systems (Table 1). The oldest and still commonly used method to deliver these compounds consists in coating surfaces by simple impregnation, by soaking a porous material or coating with the desired antibacterial compound. The lack of a particular bonding mechanism to the coating leads to fast release [25]. Delivery systems have since evolved to include a wide variety of carrier materials (i.e., any material that an antibacterial compound can be loaded in) and deposition methods. The most frequently used carriers include poly(methacrylic acid) (PMMA), polyacrylic acid (PAA), poly(lactic-co-glycolic acid) (PLGA), hydroxyapatite, polyurethane (PU), a hyaluronic acid, and chitosan [31,33]. A comprehensive review of antibacterial delivery systems can be found in [31].

A more recent approach to control the formation and release of antibacterial agents from coatings is to use polyelectrolyte multilayers (PEMs). PEMs are nanostructured polymeric systems and can be formed by layer-by-layer (LbL) deposition, which consists of the growth of alternating layers with opposite charges. This represents one of the most successful approaches to incorporate antibacterial compounds in coatings owing to its simplicity, versatility, and low cost [32]. Antibacterial agents can be either trapped between layers or constitute an integral part of the coating, by substituting one of the charged species.

Hydrogels, ceramics, and plasma-deposited polymers have also been widely reported as suitable carrier coatings for the delivery of antibacterial compounds [34–36]. The choice of coating materials ultimately depends on the chemical compatibility between the scaffold and

Table 1. Main Antibacterial Compounds in Release-Based Coatings

AB Type	Released Compounds	Mechanisms of Action	Comments[a]	Refs
Antibiotics	Aminoglycosides (gentamicin, tobramycin)	Inhibit protein synthesis by binding to the bacterial 30S ribosomal subunit		[31,119]
	Quinolones (ciproflaxin, norfloxacin)	Inhibit DNA replication and transcription, targeting DNA topoisomerases II and IV		
	Penicillins (ampicillin)	Disrupt cell wall peptidoglycan synthesis through enzymatic inhibition	Mainly Gram-positive and some Gram-negative bacteria	
	Glycopeptides (vancomycin)	Disrupt cell wall peptidoglycan synthesis by binding to amino acids	Effective against Gram-positive and mycobacteria	
	Tetracyclines (minocycline, tetracycline)	Inhibit protein synthesis		
	Rifamycins (rifampin)	Inhibit transcription by binding to RNA polymerase	Effective against mycobacteria and Gram-positive bacteria	
Antimicrobial peptides (AMPs)	Over 2000 known AMPs, both anionic and cathodic (notable examples include magainin and nisin).	Depends on the type of AMP. Include transmembrane pore formation and several metabolic inhibition mechanisms	Based on naturally occurring molecules, part of the host immune defense system	[12,120, 121]

Table 1. (continued)

AB Type	Released Compounds	Mechanisms of Action	Comments[a]	Refs
Elements (metals and non-metals)	Silver	Complete description of modes of action remain unresolved. Known to deactivate enzymes by binding to thiol groups and inhibit the respiratory chain. Contributes to ROS formation	By far the most used antibacterial metal/ nanomaterial. Together with other elements, have shown potential toxicity in human at high doses	[14,122, 123]
	Copper	Generate ROS and deplete antioxidants. Induce lipid peroxidation in bacterial membranes	Most heavy metals can induce several metal-catalyzed oxidation reactions that damage proteins, membranes, or DNA	[124]
	Zinc	Inhibit enzymatic activity		[82,91, 124]
	Gallium	Perturbs bacterial metabolism by acting as an iron mimetic		[125]
	Selenium	Unclear, likely associated with oxidative stress to the bacterial cell wall	Essential micronutrient in animals	[126,127]
	Halogens (Chlorine, iodine)	Penetrate the cell wall and disrupt protein and nuclei acids structure and synthesis		[128]
Enzyme	Lysozyme	Catalyze hydrolysis of glycosidic bonds in bacterial cell wall peptidoglycans	Effective against Gram-positive strains	[129,130]
	Acylase	Quorum-quenching	Specific for Gram-negative bacteria	[37]
Organic cationic compounds	Quaternary ammonium compounds (QAC)	Disrupt intermolecular interactions in bacterial enzymes and membranes components	Positively charged polyatomic ions of the structure NR_4^+	[131]
	Chlorhexidine	Bind to negatively charged bacterial walls, causing membrane disruption	Often used in dental or topical applications	[132]
	Octenidine	Similar to QAC		[133]
	Cationic surfactants (BAC, CTAB, DODAB)	Change the sign of the cell surface potential from negative to positive		[31,131]
	Chitosan	Still unclear. Mostly centered on the disruption of cell membrane by positively charged chitosan molecules	Antibacterial activity depends mainly on molecular weight and cationic charge density	[95]
Organic non-cationic compounds	Furanones	Interfere with key bacterial quorum-sensing and swarming pathways	Derived from marine algae	[38,134]
	Triclosan	Bind to a bacterial enzyme (enoyl-acyl carrier protein reductase, ENR), deactivating fatty acid synthesis	Recently banned in some countries for ecotoxicity issues. Endocrine disruptor	[22,112]
Other non-organic compounds	Nitric oxide	Exert nitrosative and oxidative stresses after diffusion across cellular membranes. Bacterial signaling disruptor	Short half-life (seconds), requires good control over release parameters	[80,99, 135]
	TiO_2 and TiO_2-based nanocomposites	Photocatalytically activate the production of ROS	Requires UV light. Very broad-spectrum efficacy	[109]

[a]All listed compounds have exhibited broad spectrum activity unless otherwise indicated.

the antibacterial agent, the required matrix functionalities (biointegration, wear-resistance, etc.), and the desired release modality. Because each antibacterial agent/scaffold system has unique properties, careful examination of the specific requirements for a targeted application is needed when designing release-based antibacterial coatings.

Beyond conventional biocide release, disruptors of bacterial signaling pathways have been widely explored given their ability to limit bacterial adhesion and biofilm formation. QS-inhibiting molecules incorporated in release-based coatings, including several furanones as well as enzymes, demonstrated excellent *in vitro* antibacterial properties [12,37,38]. For instance, the negatively charged acylase enzyme was immobilized on silicone catheters by LbL deposition without major loss of its enzymatic activity. The resulting coating showed a 50% reduction in biofilm formation over 7 days compared to untreated silicone, and did not present any cytotoxicity against fibroblasts [37]. Peptides have also shown potential as QS-inhibiting molecules in Gram-positive bacteria. RNAIII-inhibiting peptide (RIP) prevented *S. aureus* biofilm formation *in vivo* when released from PMMA beads [39]. Similarly, NO donors are important signaling molecules with wide-ranging functions, including biofilm dispersal due to their interaction with c-di-GMP [40]. Several NO release systems have been described in the literature, a few among them for antibacterial applications such as silica nanoparticles [41] and modified xerogels [42].

Control of Release Kinetics

The overall timeframe and kinetics of antibacterial delivery are highly application-dependent. Currently, typical release profiles follow first- or second-order kinetics, with an initial burst release followed by a decreasing tail distribution, usually ranging from hours to a few days. At first sight, a short-term, high-dose release of antibacterial agent could appear as generally desirable. It provides antibacterial protection during the early post-operation period, which is considered the most critical stage for infection risk, and limits the development of bacterial resistance. However, for implanted devices, surfaces should maintain their antibacterial properties until integration with the surrounding tissues, which can take up to several months, to prevent bacterial colonization from the hematogenous route [33,43]. Long-term release is also regularly needed in case of revision or second surgery, where tissues surrounding the primary implant are often already infected, and for near-patient environmental surfaces [14,43]. To date, designing coatings that maintain released antibacterial compounds levels within the therapeutic window, sufficient to kill bacteria but low enough to limit cytotoxicity toward eukaryotes, remains a significant challenge. Innovative approaches to control and extend release kinetics are therefore necessary to generate new solutions and products (Figure 2).

Passive Approaches

Several variables have been shown to passively influence (without active triggers) release kinetics. Engineering strategies are being developed to tune the properties of the antibacterial agent itself (concentration, distribution, size, charge, etc.), the carrier matrix (porosity, surface roughness, functional groups, etc.), or the overall micro/nanostructure of the antibacterial coating (Figure 1) [31,44,45]. Alternatively, special architectures, which possess their own tunable parameters, can be incorporated in coatings to control release kinetics. These include nanotubes (e.g., carbon or TiO_2), nanowires, dendrimers, and nanocapsules [45,46].

Nevertheless, the sustained release of poorly charged (i.e., with no polar group or few polar groups compared to its size) or small molecules is very challenging. A recent study showed that using a large polyacid core in PEMs could lead to impressive sustained release [47]. The polymer coating released physiologically-relevant drug concentrations over 14 months. Diclofenac (a nonsteroidal anti-inflammatory drug) was functionalized and conjugated to a hydrophilic PGA polymer backbone via esterification and could be released by ester hydrolysis. The observed slow release kinetics were likely caused by the high negative charge along the PGA

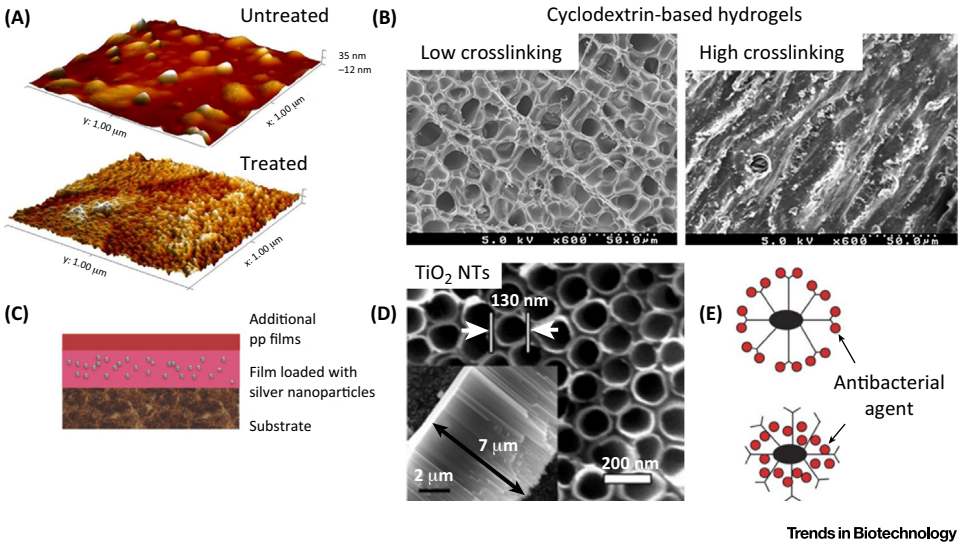


Figure 1. Schematics and Images Illustrating Various Passive Strategies to Control the Release Kinetics and Antibacterial Properties of Coatings. (A) Atomic force microscopy (AFM) images showing the change of topography and nanotexture of Ti surfaces after an acid-etching treatment [136]. (B) Scanning electron microscopy (SEM) micrographs of cyclodextrin-based hydrogels with tunable porosity [137]. Porous coatings with a lower crosslinking density exhibit faster release kinetics than more crosslinked hydrogels. (C) The deposition of a thin plasma polymer (pp) film can be used as a diffusion barrier for a release-based antibacterial coating, enabling control of the rate of release of the antibacterial agent by adjusting the thickness of the coating [138]. (D) SEM images of TiO_2 nanotubes (NTs) used as tunable reservoirs for Ag nanoparticles (NPs) [94]. (E) Other special architectures, such as dendrimers, can be used for loading and delivery of antibacterial compounds from a coating [46]. Figures reproduced, with permission, from Elsevier (A,B,D,E); ©2009 ACS (C).

backbone (caused by a polar ester group within the short polymer backbone). Negative charges are known to slow down the rate of ester hydrolysis [48]. However, the polymer–drug conjugate itself is soluble in water and cannot be used to create a stable thin film coating. The PGA-bounded Diclofenac needed to be immobilized in a PEM film, using PLL and chitosan as polycations.

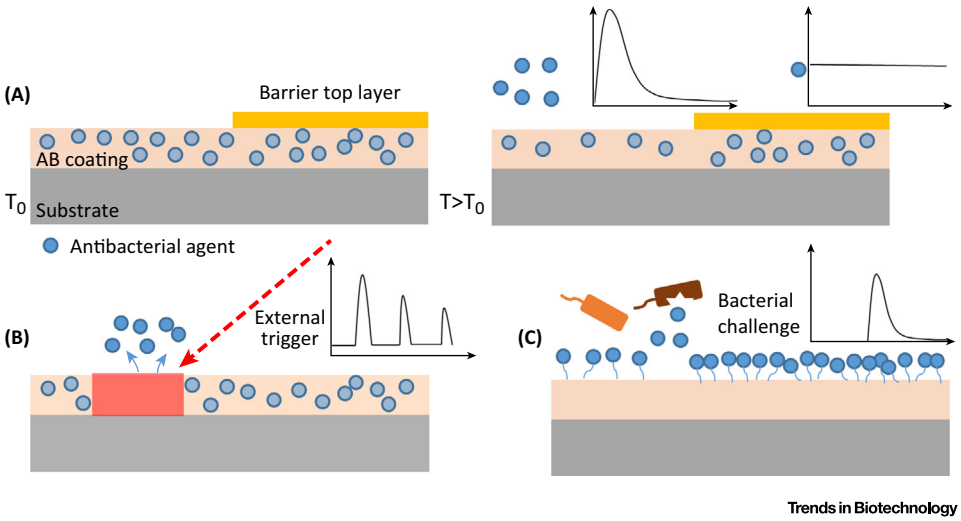


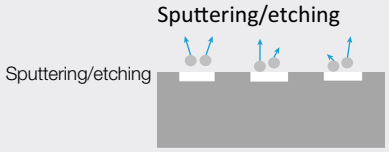
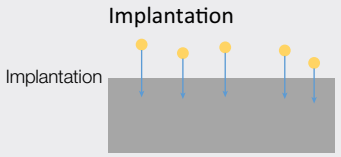
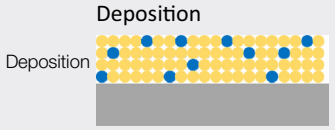
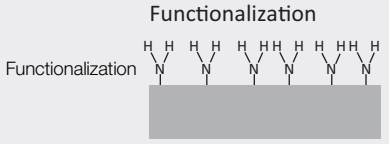
Figure 2. Designing Antibacterial Coatings within a 4D Perspective. The design strategies to control the release of antibacterial agents over space and time can be grouped under three main categories. (A) Passive approaches. By tuning the properties of the coating it is possible to impose specific preloaded release kinetics, giving the possibility to produce a variety of release profiles, including rapid bursts (left) or linear release (right) from antibacterial (AB) coatings. (B) Active approaches. External stimuli can be used to trigger the local release of embedded compounds. (C) Bacterial trigger approaches. Bacteria-responsive coatings release antibacterial agents locally when challenged by bacteria. Inset: examples of representative release profiles for each approach showing the release rate as a function of time.

Box 2. Engineering Antibacterial Surfaces Using Plasma-Based Tools

Among antibacterial surface modification and coating approaches, plasma processes currently play a relatively minor role. However, this could change rapidly with the need for alternative deposition methods to solvent-based processes and the increasing requirements for robustness and long-term stability as design criteria in antibacterial applications. Plasmas, often called the fourth state of matter, are typically generated by the ionization (dissociation) of a gas by electrical discharge. The charged particles formed, including ions, electrons, and radicals, exhibit a strong collective response to applied electromagnetic fields and can interact with and modify surfaces in several ways (Table I). Plasma-based techniques are attractive processes for antibacterial surfaces design because they combine easy preparation, great versatility, economical and solvent-free processing, compositional control, conformal and pinhole-free coverage, no thermodynamic constraints, sterility upon preparation, and the possibility for commercial-scale deposition [139,140].

The most straightforward use of plasma in the antibacterial coating field consists of using a plasma-deposited material as a reservoir for antibacterial compounds, which can be loaded either during the deposition itself or by an *ex situ* method [35]. Ion bombardment during deposition (effectively expanding the atomic intermixed zone) and graded interfaces of plasma coatings endow them with superior cohesion and adhesion compared with those deposited by wet chemistry methods. Alternatively, plasma processes can impart various functionalities at the materials surface, such as amino, hydroxyl, and carboxyl groups. These can then be used to immobilize several biomolecules with antibacterial or other bioactive properties. Because plasma processes are compatible with masking techniques, enabling surface patterning, this could be an interesting option for the development of multi-release antibacterial coatings.

Table I. Uses of Plasma Processes for Antibacterial Coatings and Surfaces

Plasma Processes	Uses for Antibacterial Surfaces	Examples, Refs
	Surface cleaning Adhesion optimization Nanopatterning Nanostructuring	[92,141]
	Introduction of different elements into the materials, providing control over: • Bioactive properties • Corrosion resistance • Mechanical properties Crosslinking and densification of polymers	[91,142]
	Thin-film coatings with AB properties Reservoir or platform for AB compounds Diffusion barrier coatings	[35,92,135,143]
	Surface activation Surface amination Formation of polar groups Immobilization of molecules	[35,110,144]

The addition of a thin polymeric top layer can act as a rate-limiting barrier to extend the duration of sustained release from antibacterial coatings. The thickness [49], degree of crosslinking (inversely proportional to the porosity) [49], and hydrophobicity [50] of the top layer were shown to be the main factors influencing the release kinetics. These techniques efficiently prevented the initial burst release and displayed instead zero or near zero-order kinetics [49,50]. A promising approach to deposit the top layer is plasma polymerization (Box 2). Alternatively, for polymeric carrier coatings, plasma post-treatments can also be used to directly induce additional cross-linking at the topmost surface of the polymer without affecting its bulk properties [51].

Active Approaches: Stimuli-Responsive Materials

Stimuli-responsive materials have been investigated in the biomedical field for several decades in applications such as self-healing coatings, micro/nano-sized sensors, and actuators and drug

release systems [52,53]. Polymers and polymer-based hydrogels can undergo volume changes (swelling, shrinking, or bending), structural transformations, or bond cleavage in response to a particular trigger, causing subsequent elution of drugs from the matrix [52,54]. These materials, however, are still seldom used as antibacterial coatings. Materials responsive to physical exogenous stimuli, which can be applied externally, offer great signal control, and are not restricted by diffusion, hold great potential for use as bioactive coatings. They have the ability to (i) produce 'on demand' antibacterial effects and (ii) extend the useful lifetime of coatings. Antibacterial release systems based on electrical, ultrasonic, photothermal, magnetic, and mechanical triggers have been reported [55–60]. The main challenges facing stimuli-triggered coatings are to achieve release of meaningful doses over multiple cycles and to minimize non-triggered background leaching from surfaces.

A promising strategy to eliminate background leaching from a poly(2-hydroxyethyl methacrylate) (HEMA) involves the control of its swelling by co-polymerizing HEMA with a hydrophobic monomer, hydroxypropyl methacrylate (HPMA), and by adding a methylene-chain coating with tunable density and organization [58]. The added layer acted as a rate-limiting barrier for both water entry and antibiotic release from the underlying hydrogel. The ultrasound-triggered release of ciprofloxacin was found to be up to 14-fold more intense than the background release rate and was repeatable multiple times, although at a decreasing dose with each pulse [58]. Ultimately, triggered-release doses and background release rates from hydrogel are interconnected because both are correlated with polymer swelling. The choice between higher delivered doses or increased control over delivery should be dictated by the potential application.

In an alternative approach, the concept of including antibiotic-producing microorganisms within a sandwich structured coating was proposed [61]. A nanoporous top membrane controls the diffusion of molecules to and from the agar middle layer serving as a habitat for *Penicilium chrysogenum*. The production of penicillin is induced by providing nutrients to the fungus. While the choice of antibacterial agent and the range of applications of this approach are limited, it could constitute one of the only truly permanent antibacterial coatings.

A major avenue that remains largely unexplored in antibacterial coatings is the use of embedded metallic nanoparticles (NPs) as plasmon-resonators for light-trigger release. Silver NPs are already widely present in antibacterial coatings and could be employed to induce near-infrared (NIR)-light triggered degradation of antibacterial agent-containing coatings, such as PEMs [62]. Alternatively, when used directly as the released compound, they may be conjugated with antibacterial-antibodies and act as cell-targeted plasmonic heaters, thus further damaging the bacteria cell membrane [63]. Nanocontainers-based smart coatings, an emerging field with great potential for controlled delivery, could also offer a versatile solution for precise and timed active release of antibacterial agents, although their development has been challenging so far [64,65]. For example, because it is a feedback-active system at the nanoscale level, our understanding of the physical phenomena involved and control of the processes are still limited. Introducing functions that survive the coating manufacture has also been a key problem.

Bacteria-Triggered Approaches

Coatings that deliver antibacterial agents only when surrounded by or in contact with bacteria represent the ultimate form of controlled release. Bacterial metabolism produces acidic substances, such as lactic and acetic acid, leading to a pH drop in their immediate environment [66,67]. Several pH-responsive antibacterial coatings have been developed by taking advantage of this phenomenon (Figure 3). Using LbL assembly, Zhuk *et al.* combined positively charged antibiotics, gentamicin, tobramycin, and polymyxin B, with a polyanionic counterpart, tannic acid, to form antibacterial PEMs [67]. In acidic conditions, the coatings release bursts of antibiotics determined by the degree of pH lowering. The driving force behind the release

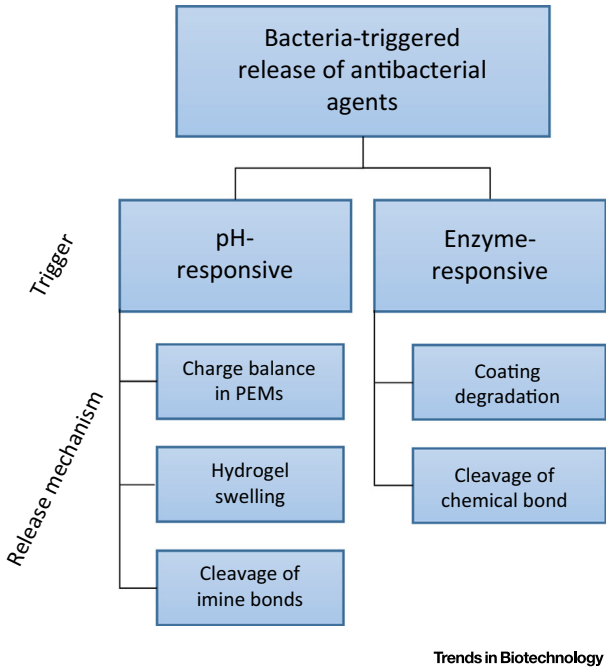


Figure 3. Control of Release Kinetics: Bacteria-Triggered Release. Coatings have been engineered to release antibacterial agents when subjected to two different bacterial triggers: the acidification of the local environment by bacterial metabolism and enzymes secreted by bacteria. When challenged, the antibacterial compounds can be released by different mechanisms from simple bond cleavage to charge balance within the coating.

was reported to be the charge balance within the PEM films. The protonation of tannic acid at lower pH creates an accumulation of positive amino groups within the film, leading to an imbalance and consequent release of the cationic antibiotics to maintain electroneutrality. The release kinetics from the coating was found to be mainly influenced by the strength of the molecular interactions.

Using similar design principles, gentamicin was combined with poly(methacrylic acid) (PMMA) and polyacrylic acid (PAA) to form hydrogel-like films with bacteria-triggered release capabilities [68,69]. The addition of anionic clay-platelets to the hydrogel matrix provided pH-independent binding sites for gentamicin, thus ensuring that a fraction of the antibiotic remained bound within the coating [69]. In all cases, the drug remained sequestered within the coatings up to several months in the absence of pH decrease or bacteria stimuli. This suggests that pH-triggered coatings could be more successful at fighting the occurrence of delayed infections than are traditional drug-eluting films. However, the coatings were not tested against repeated bacterial challenges, mostly because there is no standard protocol for such tests.

The pH-mediated cleavage of chemical bonds was also used to induce bacteria-triggered responses in coatings [70]. Gentamicin sulfate was bonded to NPs using pH-sensitive imine bonds while the NPs attach to the titanium through uncleavable amide bonds. The use of NPs allowed drug densities to be increased (2000 pmol/cm^2 with NPs vs 600 pmol/cm^2 for the standard Ti surface) and granted better versatility by facilitating modifications to include various drugs or changing the substrate material [70].

Another interesting approach consists of using bacteria-generated enzymes to degrade or cleave bounded antibacterial agents from a coating. While the pH-trigger approach cannot discriminate between different strains of bacteria, the enzymatic pathway offers the possibility to develop specific triggers for particular species. Only a few examples of enzyme-triggered release have been reported to date, and most have involved the bonding of the antibacterial compound to the substrate by an enzymatically cleavable bond. These include a thrombin-sensitive peptide

linker [71] and anhydride bonds that can be hydrolyzed by lipase [72]. A notable exception in the enzyme/cleavage pathway is the polysaccharide multilayer reported by Cado *et al.* [73]. In that case, the release of cateslytin, an antimicrobial peptide, is provided by the enzymatic degradation of hyaluronic acid/chitosan films by hyaluronidase, an enzyme secreted by pathogens. The coatings maintain their activity during three cycles of use against fresh *C. albicans* suspensions, but failed to fully inhibit *S. Aureus* after the first cycle [73].

Multifunctional Coatings

Because biological systems are inherently complex and hierarchically structured, coatings with multiple functions are necessary to achieve better performance in their environments. Recently, several multifunctional release-based antibacterial coatings have been developed; these can generally be grouped into three categories: multi-release, multi-approach, or multi-property.

Multi-Release Coatings

The co-release of antibacterial compounds with different mechanisms offers a dual advantage over single-release coatings; reduced induction of bacterial resistance and, if adequately selected, synergistic antibacterial action [74]. This paradigm has been successfully used over the years as the design principle in antibiotic-impregnated catheters [75,76]. While impregnation lacks control over release kinetics, degradable LbL assembled coatings may, on the other hand, offer a technically straightforward strategy for the pairing of controlled and combined release of antibacterial agents. Multiple antibacterial compounds can be embedded at different depths within the film and then released at different times [77]. Both the dosage and nature of the released compounds may be controlled by adjusting the chemistry of the degrading material. This scheme could be used to implement *in situ* cycling of antibacterial agents directly from biomaterial surfaces.

Silver has been successfully paired with several other antibacterial agents: antibiotics, metals, and NO- or reactive oxygen species (ROS)-generating compounds, etc. [78–82]. This could be attributed to the many modes of action of silver against bacteria, which increases the likelihood of synergistic effects. At this stage, however, direct comparisons of the effectiveness of paired antibacterial agents are not possible. Comparative effectiveness studies with a broader range of compounds will be necessary to develop and select more combinations with synergetic antibacterial properties and, ideally, no greater than additive cytotoxicity.

Multi-Approach Coatings

Unlike multi-release, multi-approach coatings do not rely solely on the release of biocides but instead seek to combine more than one antibacterial approach (Box 1) against pathogens. Coupling approaches with complementary antibacterial mechanisms, acting as multiple lines of defense, represents a promising approach to overcome the inherent disadvantages associated with each strategy.

Li *et al.* were amongst the first teams to design coatings with both release and contact-killing capabilities [83]. They combined an LbL-deposited reservoir of bilayers of PAH and PAA containing silver under a NP surface cap with immobilized QACs. The silver release from the coating provides a strong initial biocidal effect during the first few days, while the QACs retained significant contact-killing activity after the depletion of the Ag reservoir [83]. This design has since been used in a variety of combinations [32,84].

Coatings that include both biocide-release and anti-adhesion properties have also been reported [85–87]. The immobilization of PEG chains at the surface of a release-based coating represents an obvious and valid option to impart anti-fouling properties. Reduced adhesion can also be reached through non-grafting approaches such as surface patterning and modifications

of the surface chemistry. This opens up a wider range of materials and deposition techniques for the development of multi-approach coatings.

Multi-Property (Smart) Coatings

The performance and functionality of biomedical devices depends on several parameters, including for example, mechanical strength as well as resistance to corrosion and wear, to avoid failure or even dangerous consequences [88,89]. In addition, biocompatibility and resistance to corrosion and wear are two fundamental properties of implantable metals that are closely interconnected. In this framework, future generations of materials for health applications should have properties that exceed 'functional', effectively making them 'smart' [90].

Several research teams have already undertaken the development of antibacterial agent-releasing coatings with various added properties, including increased wear resistance, corrosion resistance, anticoagulation, enhanced bone-integration, and improved overall tissue-integration [91–95]. Co-delivery of other bioactive (therapeutic agents and growth factors) and signaling (quorum modulation) molecules has also been reported [72,96,97]. The various functions of nitric oxide (which plays an important role in cardiovascular systems, but can also control biofilm formation) could make NO-releasing coatings attractive options as multi-property coatings for biomedical devices [98,99]. The key difficulty in the design of such multifunctional coatings will likely be to implement functions that do not interact adversely and that can be maintained throughout the useful life of the coating [65].

Long-Term Stability

Stability, which is the capacity of a coating to maintain its properties over time, is one of the most crucial factors determining the suitability of a surface for clinical applications. It remains, however, an often-overlooked issue in the field of antibacterial coatings. Several studies have emphasized the lack of stability of some of the most popular approaches to antibacterial coatings, such as PEG-based antifouling surfaces [100,101] and LbL/polyelectrolyte films [16,32]. For example, investigations of the stability of PEG coatings in saliva, saline, and urine revealed loss of their anti-fouling properties after only 0.5, 24, and 48 h, respectively [102]. Drawbacks frequently identified in the literature to explain lackluster performances in long-term stability include chain cleavage, mechanical weakness, oxidative degradation, lack of adhesion to the substrate, and high surface reactivity leading to surface conditioning [18,101–106].

As a result, recent efforts focused on the development and assessment of robust and stable coatings. Plasma-deposited coatings emerged as a viable option; while the coatings themselves rarely exhibit any antibacterial properties, they can act as a robust carrier matrix or as platforms for immobilized bioactive molecules (Box 2). They have been found to possess superior mechanical and chemical stability compared to dip-, spray-, or spin-coated materials [35,107,108]. Polymeric materials still make up the vast majority of plasma-deposited coatings [35], but several others have demonstrated excellent antibacterial properties. These include Ag/diamond-like carbon [92], TiO_2/copper [109], AMPs/organosilicon [110] and Ag/hydroxyapatite [111] coatings.

Although a wide spectrum of antibacterial coatings has been developed over the years, and these have shown great potential in short-term *in vitro* studies, investigations of this new generation of antibacterial coatings in controlled trials are still scarce [31,105,112]. There is no doubt that the absence of studies at the clinical stage is symptomatic of the lack of emphasis on long-term stability studies in this field. At this stage, the widespread adoption of standard stability tests and the development of coherent guidelines are mandatory steps to accelerate progress towards a new generation of antibacterial coatings and their application.

Concluding Remarks and Future Perspectives

The field of release-based antibacterial coatings has developed rapidly in recent years, to become one of the most widely studied areas of biotechnology owing to their potential importance in preventing nosocomial infections. With the significant burden from biomaterial associated infections (i.e., infections related to or caused by the presence of materials such as implants, catheters, near-patient surfaces, etc.), decreasing usefulness of traditional antibiotic therapies, and growing concerns over bacterial resistance, they offer the much-needed ability to limit pathogens colonization of biomaterial surfaces by providing a local and defined delivery of antibacterial compounds.

In this review we have identified key features that must be imparted to antibacterial coatings to maximize their effectiveness and expand their area of application. Interesting questions have been raised along the way (see Outstanding Questions). Strategies for controlled release, aimed at delivering precise doses within a proper timeframe, will ultimately govern the success of these coatings. As noted earlier, bacteria-triggered release could provide the ultimate form of controlled delivery of antibacterial agents, but future research should be devoted to testing those surfaces against repeated bacterial challenges as well as to developing additional triggering pathways. Similarly, a multi-pronged approach, involving different mechanisms of action against bacteria as well as multiple integrated functions, has emerged as a crucial requirement of the next generation of antibacterial coatings. In that regard, the release of quorum-disrupting molecules paired with a potent biocide may prove to be an interesting direction to follow.

However, despite the large amount of reported antibacterial approaches in the literature, to date very few platforms have made their way to clinical studies, and even fewer to clinical practice. The lack of translational success can be attributed in part to the complexity the problem and the diversity of actors and professional cultures (researchers, physicians, regulatory agencies, etc.) [113]. An even more important factor remains that most current *in vitro* methodologies used to test antibacterial materials do not incorporate realistic *in vivo* conditions (biofouling, polymicrobial communities, relevant proteins, co-culture models, host immune response, etc.) [43,114]. Objective evaluations of coating stability, consistent with the intended application, have been similarly overlooked. Specifically structured research will therefore be necessary to develop standardized and widely accepted validation methodologies for antibacterial coatings, from which we could effectively extrapolate clinical efficacy. These should be reliable, high-throughput alternatives to clinical studies, that are also able to withstand regulatory scrutiny, because the length and cost of testing potential antibacterial surfaces in controlled human trials are prohibitive [43]. Tackling these important challenges will require a collaborative effort from researchers across disciplines to provide real advancement in the biomedical field but should offer plenty of opportunities for innovation.

Outstanding Questions

What are the health and environmental impacts of the increased use of metallic nanoparticles in antibacterial coatings for short, medium, and long-term applications?

What could justify the development of strain-specific antibacterial surfaces rather than broad-spectrum ones?

How can *in vitro* and *in vivo* testing methodologies be designed to both provide useful, standardized information and satisfy regulatory concerns?

How could regular clinical practice be changed/affected/influenced for the successful integration of new antibacterial products and solutions?

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