Received: 6 July 2022 | Revised: 2 September 2022 | Accepted: 7 September 2022

DOI: 10.1002/ppap.202200121

REVIEW

PLASMA PROCESSES AND POLYMERS

Plasma polymerization for biomedical applications: A review

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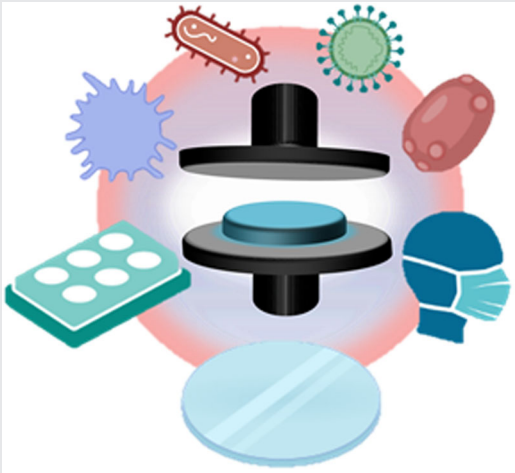
Abstract

Plasma polymers have long been of interest as thin film coatings on biomedical devices and products, to generate desirable surface properties for favorable bio-interfacial interactions. Plasma polymers have also been used as platforms for the covalent immobilization of bioactive molecules. More recently, additional aspects have been investigated, such as selective prevention of adhesion of microbial pathogens, either via plasma polymers per se or including antimicrobial drugs. Plasma polymers have also been investigated for the release of silver ions and small organic molecules. Complementing low-pressure plasma approaches, processes at atmospheric pressure have attracted interest recently, including for nano/biocomposite coatings. This contribution reviews the use of plasma polymers for intended biomedical applications, with a focus on more recent topic areas.



KEYWORDS

antibacterial coatings, biomaterials, covalent immobilization, drug release coatings, plasma polymerization

Abbreviations: AA, aerosol assisted; AP, atmospheric pressure; CDI, carbonyldiimidazole; CFU, colony forming units; DEA, diethyl acrylamide; DLC, diamond-like carbon; DMEA, diethylamino)ethylmethacrylate; EO, ethylene oxide; HMDSO, hexamethyldisiloxane; LP, low pressure; NO, nitric oxide; PE-CVD, plasma enhanced chemical vapor deposition; PTFE, polytetrafluoroethylene; PVS, polyvinyl sulphonate; TCPS, tissue culture polystyrene; PEO, polyethylene oxide; PNIPAM, poly(N-isopropyl acrylamide); TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; PDMS, polydimethylsiloxane; TEOS, tetraethyl orthosilicate; PVC, polyvinyl chloride; SDS, sodium dodecyl sulphate; ToF-SIMS, time of flight secondary ion mass spectrometry; XPS, X-ray photoelectron spectroscopy.

1 | INTRODUCTION

Plasmas, the most common form of visible matter, consist of ionized gas in equilibrium (thermal) or nonequilibrium (cold) conditions. Electrons, ions, atoms, radicals, and molecules in different states populate plasmas, which also characteristically emit UV and visible radiation. The solar corona and the Northern Lights (Aurora Borealis) are examples of thermal and cold plasmas occurring in nature, respectively. Many technologies based on plasmas have been developed over time; most of those based on cold plasmas lead to surface modification processes such as ablation (etching), treatment (grafting of chemical moieties), or deposition (plasma enhanced chemical vapor deposition [PE-CVD]) of thin coatings. Cold plasmas offer highly reactive gas environments, yet can be controlled such as not to cause substantial thermal heating, making them suitable for surface modification processes applied even to thermolabile and biological materials. Altering the surface of substrate materials with an added or ablated layer, usually tens to hundreds of nanometres thick, results in nanoscale modifications of the treated surface with no alteration of the bulk properties. Surface modification plasma processes, moreover, use minimal amounts of reactants and no solvents and thus are environmentally friendly.

Technologies based on cold plasmas have been the subject of research and development for over half a century and this has led to a number of large-scale industrial applications, with the continuing emergence of new processes and products.[1] Cold plasmas can be ignited in the lab in appropriately configured sources and reactors at low pressure (LP, typically 10–1000 mTorr) as well as at atmospheric pressure (AP). PE-CVD processes, in particular, can be applied to solid substrates in LP or AP plasmas fed with appropriate gases or vapors able to generate reactive species capable of coating the substrates with thin films, whose structure and properties highly depend on the nature of the feed and on the experimental conditions. The terminology of "monomers" and plasma polymers are typically utilized in the field to define the compounds fed into the depositing plasma and the coating, respectively. Unlike conventional polymerization methods, however, the "monomer" used for plasma polymerization does not need to be a reactive chemical compound as the plasma provides the initiation of reactions.

The unique features of plasma polymers have led to extensive research on fundamental questions such as improved control of the bulk and surface chemistries,[2,3] and a wide range of applications-oriented research and development projects towards their utility for specific intended applications. A key premise has been the ability of plasma polymers to form uniform, well-adhering coatings on a wide range of substrate materials. Another key feature is the wide range of chemistries attainable by plasma polymerization, which enables researchers to produce a highly diverse range of surface chemistries to tailor interfacial interactions with the environment that the coated product will encounter.

The ability to rationally design and produce chemistries for the control of interfacial interactions is particularly relevant to the research field of biomedical materials and devices.[4] Bulk materials suitable for the fabrication of biomedical devices, implants, biosensors, and biotechnology labware typically possess nonoptimal surface properties for interaction with the biological environments they encounter. However, by coating a bulk material or a biomedical device with a thin plasma polymer coating of appropriate composition and properties, it is feasible to produce markedly different surface chemistries and properties, and hence markedly different responses by the contacting biological environment to the presence of the synthetic, biologically foreign material. This was recognized early on and led to substantial research efforts, particularly at the University of Washington, where it was demonstrated how the response of mammalian cells varied with differences in the surface chemistry of diverse plasma polymer coatings.[5,6]

An early example of the success of plasma technology applied to biomaterials is the evolution of biological cell-growth protocols from reusable glass Petri dishes to disposable tissue culture polystyrene (TCPS) wares in the 1970s.[7] This development was enabled by the application of surface modification plasma processes to PS wares for the stable alteration of their surface from hydrophobic (poor cell adhesion) to hydrophilic (high cell adhesion) by means of plasma incorporation of oxygen-containing polar moieties.

As another illustrative example, in the early 1990s control of the surface chemistry without substantial detrimental effects on desirable bulk properties was a key design consideration in a product development that delivered enormous commercial success: extended wear contact lenses.[8] To be suitable for extended wear, a contact lens must provide sufficient flux of oxygen to the surface layers of the eye, which do not contain blood vessels. Yet, the soft contact lens materials that can achieve sufficient oxygen permeability are too hydrophobic for tear film stability. Thus, hydrophilic surface treatment or coating was required, on both sides of the contact lens. A coating is preferable to a nondepositing treatment due to the propensity of soft polymers to undergo surface rearrangement.[9] Yet, a coating produces an additional barrier to oxygen diffusion. Thus, a very thin yet uniform coating that would not

substantially reduce oxygen permeability was required. Plasma polymerization proved to be well-suited to meet these requirements.[8]

Examples from the 2020s demonstrate the speed of innovation in industrial plasma technologies applied toward healthcare materials. In response to the outbreak of the SARS-CoV-2 viral pandemic (COVID-19), the molecular plasma group (MPG) began to develop plasma coatings for nonwoven polypropylene substrates to develop virucidal face masks.[10] Over the course of 1 year, the technology was developed and rapidly scaled up to allow the industrial manufacture of coated face masks. The virucidal plasma deposited coatings were validated as being effective, without compromising mask filtration and biocompatibility standards. From the examples above, it is clear that the industrial application of plasma technologies has matured over the years to the point where rapid bench-to-industry prototyping of healthcare materials is now a possibility in certain applications.

With the ever-increasing emphasis on advances in modern science and medicine for human health care, researchers and product developers have considered plasma polymers as components of advanced products for a wide range of potential applications. This has been accompanied by much fundamental research on the physicochemical processes in plasma polymerization and their control and fine-tuning,[2,3,11] on detailed characterization of the surface chemistries and properties of plasma polymers,[12,13] and on tailoring the surface chemistries and properties of plasma polymers including optimization of the surface density of specific functional groups such as amines,[14] carboxylic groups,[15–17] aldehyde,[18,19] and ester groups.[2,3,20–23] Volatile monomers bearing the functional group of interest are utilized (e.g., acrylic acid or oxazoline[24] to produce COOH groups or aliphatic amines for NH_2 groups), and low monomer fragmentation plasma conditions (e.g., low power, pulsed plasmas at a low duty cycle, reduced ion bombardment at the surface of the substrate, etc.), for optimal retention of the structure of the monomer and incorporation of the functional group in the resulting coating. Plasma copolymerization (using a feed stream of two different monomers) has also been used to generate specific surface chemistries.[25] Biomimetic surfaces for direct cell attachment and/or immobilization of biomolecules (e.g., peptides, saccharides, enzymes, etc.) are usually the final goal of such surfaces,[26–28] whose stability in water has to be optimized and checked, due to their applications in aqueous media.[29–32]

The use of plasma polymers for implemented and intended biomedical applications has been the subject of a number of excellent reviews.[33–37] Accordingly, we will touch only very briefly on some of the "older" applications for which the concepts are well-known and recent advances have not included conceptual breakthroughs but, rather, been incremental (though often highly relevant to specific applications). The main focus of this review is on some topics and intended applications where much of the work is fairly recent and there has been significant progress over the last decade.

2 | BIOMEDICAL APPLICATIONS

2.1 | Attachment of mammalian cells

For many biomedical applications, cells need to be able to attach and adhere to the surface of synthetic material, device, or implant, and then spread and exercise metabolic activities without substantial compromise to their functionality. Examples range from cell culture in laboratory glassware to biomedical implants where human tissue needs to attach to the implant surface and achieve bio-functional integration. It was recognized early on that a number of plasma polymers can serve as excellent support surfaces for the attachment of viable cells and tissue.[5,6] More recently, interest has expanded to the development of scaffold constructs for tissue engineering and regenerative medicine, and plasma polymers again can provide excellent surfaces for cell attachment. In this context, double plasma polymerization and/or grafting processes proved to be efficient in creating gradients of hydrophilicity and cell-adhesion properties from the outside (less adhesive) through to the inside (more adhesive) of the scaffolds, capable of improving the quality and the rate of cell colonization.[38–40] While it is more complex to analyze a coating on a 3-D scaffold, for example, to ascertain uniformity, the concepts and plasma polymers used are the same as those that are well known for the achievement of cell attachment onto 2-D surfaces. Thus, the coating of scaffolds usually can be guided by previous work with flat substrates. Of course, there are additional challenges such as the need to engineer plasma processes to cope with complex 3-D geometries that require penetration of species into the porous structure of scaffolds. These challenges have been addressed in low and AP plasma processes, as reported in several papers.[38–47] Plasma functionalization of 3-D scaffolds is a research area of considerable current interest in regenerative medicine.

2.2 | Nonfouling and switchable plasma polymers

In contrast to the exquisite specificity of biomolecular processes, interactions between synthetic materials

surfaces and a contacting complex biological medium, such as blood or tissue, typically are nonspecific in the sense that they involve a number of proteins, as well as lipids and other biomolecules, and hence are challenging to predict and control. Most proteins adsorb readily onto a wide range of synthetic surfaces, and thus it is not surprising that adsorbed layers of biomolecules comprise a substantial diversity of proteins (as well as lipids in the case of contact lens fouling). The nature and time sequence of protein adsorption from blood has been studied extensively.[48–50]

There has been a large body of research on approaches to prevent the adsorption of all biological entities onto the surface of materials; hence "nonfouling" coatings have been the subject of much interest. For example, for biosensors aiming to detect a specific marker of disease, it is essential to prevent other biomolecules from adsorbing and thereby producing a background noise. Likewise, prevention of adsorption of proteins initiating blood clotting is a requirement of synthetic small-diameter blood vessels. Plasma polymers have also been studied for their suitability for such applications.

Coatings comprising highly hydrated, flexible polymers such as polyethylene oxide (PEO) have led to surfaces with very low, barely detectable residual protein adsorption; it is conceivable that for such coatings the limit is not the intrinsic properties of the surface but some coating defects. Plasma polymers are well known for high coating uniformity and thus might be well suited for nonfouling applications. This has led to the development of PEO-like plasma-deposited coatings,[51,52] where the density of unfragmented $-CH_2CH_2O-$ EO moieties of the monomer is kept very high in the plasma polymer by tailoring the deposition parameters (e.g., feeding a monomer with the highest possible number of EO moieties, low power input, highest possible pressure, pulsed discharge, low ion bombardment on the substrate, etc.) such as to limit the fragmentation of the monomer in the plasma process. LP processes were utilized first to deposit this class of coatings[51,52]; more recently, AP plasma processes have also been developed using EO monomer for depositing PEO-like plasma polymers[53] and also combined with an aerosol-assisted method using EO[54] or PEO polymers in solution[55] as feed.

While PEO-like plasma polymers did exhibit substantial reductions in protein adsorption, there was a fundamental dichotomy that needed to be addressed: plasma polymers that are highly hydratable also tended to partially or entirely dissolve in aqueous solutions. More complex coating procedures have been used to address this issue, for example by using a multistep deposition and baking procedure[56] or using an AP plasma to first deposit a primer layer from ethylene followed by deposition of a graded coating by gradually reducing ethylene monomer while increasing EO monomer.[54]

In a similar vein, plasma polymers mimicking poly (N-isopropyl acrylamide) (PNIPAM), a polymer that can be thermally switched between adsorbing and repelling proteins and cells, have also attracted attention.[51,57] As originally reported, pp-NIPAM coatings did not fully match the performance of PNIPAM coatings produced by conventional polymerization approaches with a differing magnitude of moduli and swelling ratios demonstrated.[51] An advancement with thermoswitchable plasma-polymerized monomers has since been demonstrated. Using atmospheric plasma deposition of vinylcaprolactam (NVCL) and ethylene glycol dimethacrylate (EGDMA), Moreno-Couranjou et al. demonstrated good thermoswitching behavior of formed copolymer deposits which improved thermoswitchable protein antifouling performance.[58]

2.3 | Antimicrobial coatings

This area of research has received considerably increased attention in recent years on account of the increasing incidence and awareness of biomedical device-associated infections. Such infections are caused by microbial colonization of surfaces and subsequent biofilm formation; bacterial or fungal pathogens, or mixed populations, can be involved.[59] A wide variety of products are known to be subject to infection, from surgical tools and contact lenses to implants. In the case of the latter, treatment can be complicated and require repeat surgery.

Accordingly, there has been a large body of research aiming to understand the mechanisms of colonization of synthetic surfaces by microbial organisms and developing surfaces and coatings resistant to colonization and/or biofilm formation.[59] Not surprisingly given the ease with which plasma polymers can coat a wide variety of materials, they have received attention for this purpose. Three previous reviews on plasma polymers for antibacterial coatings[60–62] discussed the state of the art in 2011 and 2016; accordingly, here the focus is on the more recent literature.

2.3.1 | Plasma polymers with inherent antimicrobial properties

The most straightforward approach toward manufacturing consists of the deposition of a plasma polymer film that has intrinsic antimicrobial properties, as opposed to

those systems where the plasma polymer serves as an interlayer for further modification. For example, a number of chlorinated organic compounds are known to have antiseptic properties, and therefore deposited plasma polymer films formed from chlorinated compounds may possess inherent antimicrobial properties.

Michl et al. conducted a systematic plasma deposition study of small molecular weight chlorinated hydrocarbon compounds of the form C_xCl_y where the number of carbon (x) and chlorine atoms (y) varied from 1 to 4.[63] For each of the nine compounds tested, evaluations of the antibacterial performance (vs. *Staphylococcus epidermidis*) were correlated with the precursor compound's Cl/C ratio. Surface polymers formed from multiply substituted chlorinated compound precursors (where the Cl/C ratio was greater than 1.5) showed improved antibacterial surface performance, whereas ratios less than 1 had poor performance. The most promising antimicrobial plasma polymer, formed from 1,1,2-trichloroethane (Cl/C ratio 1.5), has received the most attention. After extensive soaking and washing of the surfaces, investigators discounted the surface-release of compounds as a mechanism of action. The postulated mechanism of action was that noncrosslinked chlorinated oligomers partition at the interface and act to destabilize bacterial membranes. Plasma polymers from 1,1,2-trichloroethane exhibited not only antibacterial[64] but also antifungal properties, in that coatings were effective in controlling fungal cell growth on surfaces from the two common human fungal pathogens *Candida albicans* and *Candida glabrata*.[65]

Despite its molecular simplicity, nitric oxide (NO) is a biologically important signaling molecule involved in a range of vertebrate and microbial biological processes; it is known to impact bacterial quorum sensing and growth.[66] As NO needs to diffuse into and within biological systems for activity, an active coating must be capable of releasing it at a sufficient rate. This was achieved by plasma polymerization of isopentyl nitrite, which resulted in deposited layers capable of releasing NO.[67] Against *S. epidermidis*, released NO delayed their growth, but did not kill adhering bacterial cells. It was speculated that such bacteriostatic behavior may be of clinical benefit as a coating for medical devices which can slow down bacterial biofilm formation in a critical postoperative time window, allowing innate immunity to then neutralize "stunned" pathogenic microbes.

While low-boiling organic liquids have often been investigated as convenient precursors for plasma deposition, it is also possible to generate organic vapors from volatile solids (at room temperature). TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, is a 156 g/mol organic solid compound notable for the presence of a stable NO radical and its ability to sublime at relatively high pressures. Plasma polymers deposited from sublimated TEMPO[68] were found to produce a number of different hydrocarbon fragments, which formed plasma polymer coatings but were lacking in higher functionality. However, it was discovered that controlling the vapor pressure of sublimated TEMPO before striking the plasma resulted in deposits that retained nitrogen and oxygen, along with the stabilizing methyl substituents, which produced the characteristic unpaired electron of the parent compound. In antimicrobial assays, such plasma-deposited TEMPO coatings were observed to slow down surface colonization of the human pathogens *S. epidermidis* and *C. albicans*.

In the late 2000s, a number of studies investigated intrinsically antibacterial plasma polymers formed from essential oil precursors in LP plasmas, as previously reviewed.[60–62] Since 2014, research has explored the antibacterial properties of plasma polymer coatings formed from other essential oils and plant secondary metabolites. Pegalajar-Jurado et al. deposited plasma polymer coatings of 1,8-cineol and evaluated their performance against *Escherichia coli* and *Staphylococcus aureus*.[69] A significant reduction in bacterial adhesion (compared to hydrophilic controls) was observed for *S. aureus*, but amounted to less than log 1 reduction, which may not be sufficient for clinical viability. For *E. coli*, the reduction was closer to log 2.

Mann et al. performed experiments to study plasma deposited cineol coatings against the same bacterial species,[70] evaluating antibacterial performance by the percentage surface coverage of biofilm. The best performing films reduced coverage (compared to controls) by 35% for *E. coli* and 45% for *S. aureus*. This study showed that the amount of biofilm coverage inversely depended upon the water contact angle of the surface coatings, since, when the cineol films were treated with water plasma, the water contact angle decreased whereas the bacterial biofilm coverage increased. Similarly, Chan et al. plasma polymerized the essential oil terpenoid carvone.[71] The plasma polymer decreased the number of attached *E. coli* and *S. aureus* cells by log 1 or less.

Geranium oil is a mixture of organic compounds possessing many different chemical and structural-functional groups. A 2017 publication by Al-Jumaili et al. characterized plasma polymers films formed on glass substrates using geranium oil precursor and antibacterial performance evaluated against *S. aureus*, *Pseudomonas aeruginosa*, and *E. coli*.[72] While bacteria were shown to colonize the plasma polymer coatings, the adherence was less for films deposited using 10 W power compared to 50 W power, which illustrated an antiadhesive effect against these bacteria. In follow-up work from

the same group, a one-step procedure enabled simultaneous vaporization of geranium oil precursors and zinc acetylacetonate using thermal decomposition. This method resulted in mixed organic/inorganic plasma polymer films.[73] Live/dead staining revealed that a percentage of *S. aureus* and *E. coli* cells were dead on the surface, but, while significantly decreased in the Zn/Ge system, the number of live bacterial cells remaining amounted to less than 1 log reduction. Subsequently, the co-deposition of zinc acetylacetonate and terpinen-4-ol was used to fabricate surfaces whose antibacterial performance was evaluated against *E. coli*.[74] The percentage reduction in CFU (compared to controls) was about 40%–70% for the terpinen-4-ol polymerized coatings alone whereas incorporation of the zinc component increased this to about 85%. The antibacterial mechanism was postulated to have both a releasing and a contact-mediated action.

Plasma polymerization of terpinen-4-ol was revisited by Kumar et al. as a one-step coating technique to form antibacterial surface coatings.[75] Antibacterial testing using *P. aeruginosa* showed the presence of dead cells on the coatings and a significant reduction in live bacteria. However, the overall performance of the coatings, as judged by the reduction of live bacteria on the surface, equated to a reduction in the surface density of live bacteria of only ~ log 1.

Besides essential oils, organic phosphorus compounds have been investigated. Kaleli-Can et al. deposited a plasma polymer coating from the precursor diethyl phosphite.[76] Using the JIS Z 2801 standard test for antimicrobial activity of plastics, antimicrobial results were reported for *S. aureus* and *C. albicans*. Compared to controls, antibacterial and antifungal performance was modest showing an ability to eliminate 150 CFU/ml for *S. aureus* and 60 CFU/mL for *C. albicans*.

Another class of plasma polymer coatings that exhibit intrinsic antibiofouling properties are those pioneered by Vasilev and co-workers and a based on films deposited from oxazoline precursors such as 2-methyl-2-oxazoline and 2-ethyl-2-oxazoline.[77–79] After careful optimization, the oxazoline-based coatings are capable of achieving a reduction in biofilm formation of up to 90% relative to control Thermanox or glass slide.[78,80] The possibility to retain low biofouling properties was also demonstrated when oxazoline precursors were deposited at AP.[81]

These reports demonstrate the possibility of significantly reducing bacterial adhesion on surfaces (compared to control biomaterials) for bacterial and fungal pathogens of significant human concern. A favorable aspect is that at least five of these reports also evaluated the human cell compatibility of the plasma polymers.[67–69,71,76] However, questions remain about whether one-step plasma polymer films will be sufficiently effective as a clinical infection control measure. With activity typically resulting in ~90% reduction in bacterial adhesion to surfaces, this must be considered against the perspective that microbial pathogens can number in the hundreds of thousands or in the millions, and are capable of exponential growth in a number of hours, the question is whether a 90% (log 1) reduction of attachment of pathogens would be a clinically relevant benchmark for the performance of such coatings. Indeed, the biomedical device industry interest seems to look for a log 3 (99.9%) reduction. It is worth mentioning, though, that colony-forming units are not the whole story, as biofilms represent a significant clinical challenge. In addition to reducing attachment, biomolecular interference with biofilm formation and maintenance might be necessary to achieve clinical viability.

Nearly all of these reports concluded that the antibacterial mechanism was unclear. When the organic chemical precursor compounds show high bacterial toxicity (i.e., several orders of magnitude activity) in solution, why does this activity not seem to manifest as well in surface coatings, where activity typically is only 1 order of magnitude inhibition? A few of the above studies of plasma polymerized essential oils used 1,7-octadiene plasma polymerized coatings as a control surface.[69–71] While inhibition on octadiene plasma polymer surfaces was shown to be less than on the intended antibacterial surface coatings, on a log scale, their activity is of the same order of magnitude (1 log or less). In other words, for nonreleasing surfaces, there is a discrepancy of orders of magnitude between solution and surface activity, and the antibacterial activity of plasma polymers from essential oils is comparable to that of plasma polymers from simple hydrocarbon (nonfunctional, i.e., octadiene) plasma polymers. There is good evidence, and it has been noticed, that the relative surface free energy of these coatings seems to correlate with activity. Thus, it might be speculated that the scrambling of molecular structural elements during plasma polymerization eliminates biologically important, specific molecular structural elements of these compounds. Nonspecific chemical properties of the precursor compounds (their polar and nonpolar groups) lead to hydrocarbon backbone plasma polymers with some functional groups but not retained full molecule structures. Hence their antibacterial surface performance (attachment and inhibition) amounts only to mild inhibition, not mimicking the activity of, for example, terpene structures of freely diffusing essential oil compounds. The release of oligomeric hydrophobic fragments might also contribute to the observed moderate antibacterial activity. Further studies of as-deposited plasma polymer coatings versus

thoroughly solvent-extracted coatings should be carried out to investigate this question.

2.3.2 | Antibiotics released from plasma-deposited polymer layers

Compared to nonspecific antiseptics and small molecules, clinically approved antibiotics are prized for their potency while usually remaining well-tolerated by human and animal patients. For example, solution concentrations on the order of submicrogram/ml of drugs are capable of microbial inhibition on the order of 10^6–10^8 planktonic colony forming pathogenic cells. Thus, the release of small concentrations of such drugs from plasma polymer films could be a way to locally inhibit potential microbial colonizers of medical device implants, and due to the extremely high molecular activity of such drugs, it might be feasible to store sufficient amounts even within thin plasma polymer coatings.

Los et al. formed antibiotics-releasing layers by nebulizing ampicillin or gentamicin in a reaction chamber and simultaneously striking a helium plasma.[82] The procedure was repeated up to nine times to form stacked layers on various substrates. When deposited in microtiter plates, such layered structures prevented planktonic bacterial growth (*E. coli* and *P. aeruginosa*) for 24 h and also prevented biofilm formation. Unsurprisingly, the released antibiotics were highly bactericidal, eliminating 10^6 colony-forming units. The advantage of this deposition technique is that no linker chemistry is needed and the system can be formed in a one-step process.

Naderi et al. prepared a water-stable heptylamine plasma polymer coating approximately 100 nm thick which acted as a reservoir for loading and releasing the antifungal drug fluconazole.[83] Activity against *C. albicans* was assayed using three different microbial assays: the agar diffusion method, a contact-kill method, and static biofilm assay. Antifungal activity was measured to be of the order of 2 logs. It was postulated that this performance was limited by the limited ability of the plasma polymer layer for imbibing higher concentrations of the antifungal drug.

The deposition of drug release coatings loaded with vancomycin and gentamicin antibiotics using aerosol assisted-AP-PE-CVD has been reported.[84,85] Under specific experimental conditions this approach enables the deposition of bio/nano-composite coatings consisting of nanometric spherical capsules with the biomolecules located inside a plasma polymer shell, embedded in a plasma polymer matrix, as shown in Figure 1. In such plasma-deposited drug-release coatings the leaching rate of the drug in selected water media can be further regulated by means of a plasma polymer of appropriate

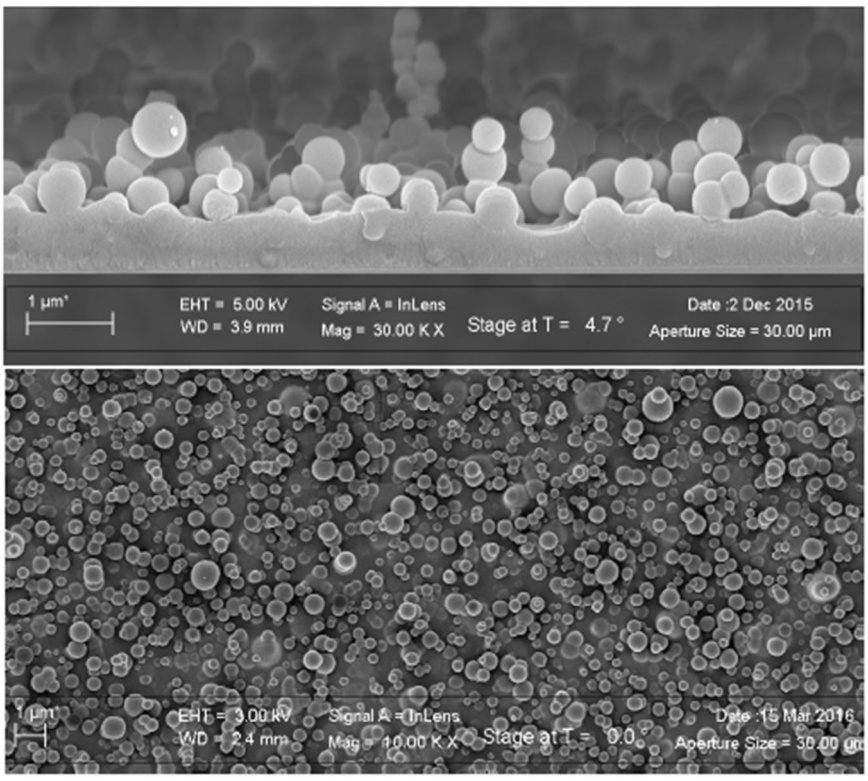


FIGURE 1 Side view and top view SEM images of an aerosol assisted-atmospheric pressure-plasma enhanced chemical vapor deposition deposited nano/bio composite coating made of nanometric capsules embedding vancomycin. A dielectric barrier discharge reactor was used, fed with He, C_2H_4, and aerosol of a 10 mg/ml of a water/vancomycin solution.[84]

thickness and properties deposited on top of the drug-containing coating.[86]

In addition to the above examples of embedded organic antibiotic drugs, plasma polymers have also been used for the incorporation of (inorganic) metal atoms and metal ions that kill bacteria. As for the organic drugs, metal ions can be added to the plasma polymer carrier layer simply via in-diffusion from an aqueous solution, as discussed further below (Section 2.4). Other approaches have also been investigated; of interest is a single-step approach using LP PE-CVD processes combined with sputtering of metals with antibacterial properties (e.g., Ag, Cu, and Zn). Under optimized conditions, this has allowed the deposition of nano-composite coatings. The network of the coatings (PEO-like, silicone-like, silica-like, etc.) is generated by the fragments of the monomer feeding the plasma, while the nanometric metal clusters embedded in the network originated from the sputtering process. When the network is synthesized with sufficient stability and water-absorbing properties, antibacterial metal ions are released by the metal clusters in aqueous conditions.[87,88] The large majority of such studies have focused on Ag nanoparticles or Ag^+ ions, and the combination of Ag and plasma polymers is discussed further below in Section 2.4.

2.3.3 | Plasma polymers as barrier layers for controlling release rates

Instead of incorporating antimicrobial drugs into plasma polymers, another approach consists of depositing a plasma polymer layer on top of a layer of antimicrobial drug molecules, with the thickness, structure, and properties of the plasma polymer then controlling the rate of diffusion of the drug molecules through the plasma polymer and hence the release rate. One example is discussed in the preceding section.[86]

One of the first examples of this approach consists of deposition of levofloxacin from solution by drop casting onto a substrate with tailored wetting properties to form droplets of desired dimensions.[89] The levofloxacin particles that formed after the solvent evaporated were coated with a heptylamine plasma polymer layer with controlled thickness. The study demonstrated that the release rate of the antibiotic can be effectively controlled by the thickness of the barrier payer.

Dowling et al. designed a sandwich approach by layering tetraethyl orthosilicate (TEOS) on polystyrene, applying a nebulized spray layer of the antibiotic rifampicin, followed by a plasma polymer overlayer of polydimethylsiloxane (PDMS).[90] If the base layer of TEOS was deposited such that it contained a higher-surface area nanostructure, then the rate of release of the drug could be tuned. While the release kinetics of rifampicin was studied, and layers were also deposited onto polyvinyl chloride (PVC) tubing, the antibacterial performance of these surfaces was not reported.

Vasani et al. used plasma polymers from 1,7 octadiene and acrylic acid to create a barrier coating for controlling drug elution from drugs loaded inside the pores of porous silicon substrates.[91] The active drug compound was levofloxacin, a broad-spectrum antibiotic. Since the polymers used to cap the pores could undergo reversible swelling when exposed to buffers of different pH (5 and 8), the release of levofloxacin from the porous silicon matrix was influenced by changes in pH. Fast drug release was observed for solutions of pH 8. Bacterial assays were conducted versus *P. aeruginosa*. To study bacterial inhibition, solutions released from the substrates were removed and inoculated with bacterial cultures and an 80% reduction in growth was observed. In a related report, Schultz et al. used the porous silicon/octadiene plasma polymer system but included an additional plasma polymer layer deposited from diethyl acrylamide (DEA) or diethylamino)ethylmethacrylate (DMEA).[92] The DEA-coated system released more levofloxacin when pH switched, however, the DMEA system released more levofloxacin in general. It was found that the DEA layer acted like a temperature switch whereas DMEA acted like a pH switch.

A plasma-coated barrier layer can also be applied to the surface of drug particles. For example, Cavallaro et al. utilized a plasma system where off-the-shelf drug powders are placed on a continuously moving platform, which allows for the particles to be uniformly coated and encapsulated in a plasma polymer layer.[93] As a demonstration, the authors encapsulated highly hydrophilic ampicillin powders in a relatively hydrophobic 1, 7-octadiene-based plasma polymer layer. The thickness of the plasma polymer capsule allowed for tuning the release rate of the antibiotic. While highly hydrophilic ampicillin powders almost instantly dissolve in an aqueous medium, the application of a 1,7-octadiene-based plasma polymer capsule could extend the release for up to 5 days. Importantly, the authors demonstrated that the antibacterial potency and MIC of ampicillin were retained after encapsulation and release.

A recent study described how plasma polymer coatings could be used in combinations with sputtered coatings of titanium dioxide and silver "nano islets" on substrate materials relevant to biomedical device manufacture.[94] Such hybrid catalytic surfaces in themselves showed good inhibition against *E. coli* and *S. aureus*. However, an additional modification was applied in the form of a 4-nm thick plasma polymerized HMDSO

coating. This helped to suppress silver dissolution while also changing surface wettability. The HMDSO coated samples maintained good antibacterial action against *E. coli* using an agar touch method.

2.3.4 | Grafted peptides

Plasma polymers bearing reactive chemical groups on their surface can be used for convenient covalent immobilization (grafting) of bioactive molecules such as naturally occurring antimicrobial peptides. To avoid denaturation of peptides (and proteins) it is desirable to perform grafting under mild, aqueous solution conditions. Interfacial reactions such as carbodiimide-mediated formation of interfacial amide bonds, spontaneous condensation between aldehyde and amine groups followed by reduction (reductive amination), and reaction between epoxy groups and amines are particularly well suited.[95]

Using reductive amination (amine groups on the peptide and surface-active aldehyde groups) for grafting, Griesser et al. investigated the immobilization of the antimicrobial peptides LL37, magainin 2, and parasin 1 onto propionaldehyde plasma polymer surfaces.[96] Antibacterial testing versus *S. epidermidis* showed, using live-dead cell staining, significant numbers of dead, attached cells to surfaces of all three peptides where the magainin 2 surface had the best antibacterial performance, followed by LL37 and then parasin 1 surfaces. On the aldehyde plasma polymer, *S. aureus* and *E. coli* were found not to attach very well, which made determination of the effect of the grafted peptides more difficult to gauge. The peptide-attached surface coatings were found to be compatible with the attachment and survivability of primary human fibroblasts.

2.3.5 | Grafted antimicrobial drugs

A variety of highly active antimicrobial drugs has been developed by the pharmaceutical industry, but applying them to surface coatings has not been straightforward. It might be asked whether permanently tethering antimicrobial drugs to surfaces could result in effective inhibition similar to that seen in solution studies of drugs with high antimicrobial potency and long-lasting prevention of biofilm formation (as opposed to the limited duration of diffusive drug release). Obviously, for a surface-grafted drug to be active, it must target a ligand on the surface of a microbial organism rather than acting via an intracellular mechanism such as inhibition of bacterial gyrase enzymes. A key issue to study is whether the surfaces are truly active in this way, or whether an unintended or unnoticed release or out-diffusion of drug molecules could cause misinterpretation of the mechanism of action.

Coad et al. deposited plasma polymerized propionaldehyde coatings to conjugate the amine-bearing antifungal drug caspofungin using reductive amination.[97] A set of experiments was designed to validate a washing protocol that could differentiate whether the compounds were covalently attached or physisorbed and then released diffusively. Grafting of two structurally similar antifungal drugs from the same drug class (anidulafungin and micafungin) was attempted; however, these compound lack primary amine groups and therefore the required nucleophiles capable of forming covalent bonds to surfaces. When moderate surface washing was used after the coupling protocols, surfaces prepared with all three compounds retained antifungal properties; however, washing the surfaces with a surfactant (sodium dodecyl sulfate [SDS]) disrupted the noncovalent, physisorbed surface affinity of the nonreactive compounds and removed them from the surface, eliminating the antifungal surface performance. Only the caspofungin surface coating retained antifungal activity after SDS washing, attesting to covalent grafting. Furthermore, the presence or absence of the three antifungal compounds on the surfaces was confirmed by XPS and ToF-SIMS. Caspofungin-grafted surface coatings were observed to inhibit fungal cells for the human pathogens *Candida tropicalis*, *C. albicans*, *Candida parapsilosis*, and *C. glabrata*. Subsequently, the antifungal activity of caspofungin-grafted surfaces against drug-susceptible and drug-resistant strains of the recently emerged, concerning human fungal pathogen *Candida auris* was also evaluated.[98] Using live-dead cell staining, it was confirmed that fungal inhibition resulted in fungal cell death; conversely, the absence of toxicity of the coatings toward human fibroblasts was confirmed.[99] The nontoxicity of caspofungin to human cells and high lethality to fungal cells are well-known solution properties of this clinically approved antifungal drug: it selectively inhibits an enzymatic pathway present in fungal cell walls, which is naturally absent in mammalian cells. Fungal attachment inhibition by caspofungin surface coatings was observed to be around log 6 against *C. albicans*, and this completely prevented biofilm formation.

Besides aldehyde plasma polymer coatings, covalent attachment could be facilitated by linking caspofungin's amine groups to epoxide groups present on plasma polymers from continuous and pulsed deposition of allyl glycidyl ether[100] or glycidol.[101] The latent reactivity of intact epoxide groups on these plasma polymers allowed for strong covalent bonds to be formed without the need for a second chemical step.

Straightforward covalent coupling of antimicrobials can also be mediated by ion-assisted plasma polymerization.[102] Akhavan et al. showed that pulsing a mixture of acetylene, nitrogen, and argon gases resulted in a thin-film deposit containing long-lived radicals that facilitate the covalent coupling of molecules via radical reactions. The antifungal effect of such grafted coatings was demonstrated for caspofungin against *C. albicans*, and an antibacterial effect was also demonstrated for the peptide Mel4 against *S. aureus*. The antifungal potency was observed to eliminate 10^7 colony-forming units. The antibacterial evaluation showed a reduction in the surface coverage of attached cells where the remaining colonization on the antibacterial surface coating was about 7.5% live cells and 5% dead cells.

Not all antimicrobial drugs grafted to surfaces show an effective demonstration of surface activity, nor should they if inhibition cannot occur because the antimicrobial drug fails to meet its target. Polyenes are a class of antifungal drugs whose target of inhibition is located in the fungal cell membrane, not in the fungal cell wall as was the case with caspofungin. Naderi et al. grafted five drugs from the polyene class of antifungal drugs onto propionaldehyde plasma polymers, with coupling facilitated by reductive amination.[103] While water-rinsed samples exhibited antifungal activity, after washing with SDS none of the surfaces demonstrated any antifungal activity. When less thorough washing was used, however, high surface activity was observed, in one case causing a log 6 reduction. The combined results showed that antifungal activity was solely due to physisorbed drug molecules being able to desorb off the surface into fungal cell membranes, whereas after SDS washing the remaining covalently grafted drug molecules, detected by XPS, failed to provide activity. This report demonstrated an important but often overlooked caveat: when grafted antimicrobial surface coatings are not washed thoroughly after drug immobilization, observed activity might not be due to (covalently) surface-grafted molecules but be caused by released physisorbed molecules, and hence a misinterpretation of the mechanism of action could result in the absence of systematic testing after washing protocols, and surface analysis.[103]

Plasma polymer coatings fabricated using ethanol and propionic acid provide alternative platforms onto which antimicrobial compounds can be immobilized. XPS analysis of these surfaces shows oxygenated groups such as −OH and −COOH to which antimicrobial compounds bearing −OH, $-NH_2$ substituents can be coupled using carbonyldiimidazole (CDI).[104,105] After thorough washing (again using hot SDS solution), Naderi et al. showed that surface-attached caspofungin, anidulafungin, and micafungin all showed potency in eliminating 10^6 CFU/cm^2 of *C. albicans* cells and prevention of biofilm formation. The hypothesis that covalently attached drugs could form a "permanently" active antimicrobial interface was tested by reusing the surfaces in repeat antimicrobial assays with fresh microbial challenges. Results showed that the anidulafungin-attached surface could be challenged at least five times while eliminating colonizing cells and preventing biofilm formation.[105] This study demonstrated that grafted antimicrobial coatings have the potential to achieve longer-lasting deterrence than release coatings can.

Finally, a recent study focussing on grafted antibacterial agents described gentamicin and the antibacterial peptide indolicidin on a polymer coating generated from plasma-activated Ar, CO_2, and C_2H_4 gases.[106] Covalent attachment was facilitated by EDC/NHS coupling of the primary amine-bearing compounds to COOH groups present on the plasma polymer. It was found that the covalently attached compounds gradually released over time, and this was found beneficial in extending the release profile of the agents. Performance was measured against *E. coli* where inhibition was of the order of 10^4 to 10^5 CFU/ml.

2.4 | Silver-containing plasma polymer films

Over the last three decades, silver, silver salts, and silver nanoparticles have been of great interest to researchers and medical and industrial communities for application on medical devices, textiles, and other surfaces to render the surface antibacterial.[107–110] The interest in silver stems from the capacity of the metal ion to kill both Gram-positive and Gram-negative bacteria, fungi, and even viruses. More importantly, silver has a multifaceted antimicrobial mechanism of action, which involves simultaneous targeting of multiple sites of the bacterial cells including the membrane, DNA, proteins, and enzymes.[108] As a result, it is more difficult for bacteria to develop resistance to silver compared to common antibiotics, which generally target only a single site.

The scientific, commercial, and clinical need for silver-containing coatings inspired plasma polymer-based approaches contributing to this still-growing area.[60,62,111] In this relatively short section, it is not possible to review every single report, nor is it its purpose. The aim is, rather, to give the reader a taste of the possibilities offered by plasma-based technologies. Silver-containing plasma-derived coatings can be deposited both at low (under vacuum) and at AP. Although processes carried out under vacuum provide greater control over coating structure and

functionality, AP techniques are more attractive for large-scale continuous manufacturing processes. In the following, the methods for generating silver-loaded films are separated into direct and multistep approaches, and relevant examples given.

2.4.1 | Direct deposition

The beginning of the direct methods of deposition can be traced back to the work of Favia et al.[112] where silver nanoparticles were embedded in PEG-like plasma polymer films. The method involved plasma polymerization of diethylglycol-dimethyl-ether with simultaneous sputtering from a silver electrode.[112] Such coatings have proven to be effective against a range of pathogenic bacteria, including those relevant in the food industry.[113] This plasma polymerization/sputtering approach was also utilized by several other groups to deposit polymer/silver composite coatings using a variety of organic precursors (HMDSO,[114] polyaniline[115]) and gases/gas mixtures (NH_3/C_2H_4,[116] CO_2/C_2H_4,[116] C_2H_2[117]). Silver sputtering in the plasma phase was also used to produce diamond-like carbon (DLC) coatings containing silver nanoparticles.[118,119] The advantage of DLC coatings is their mechanical rigidity, which can benefit certain applications where softer polymer-like films may not be applicable.

Another elegant direct approach is the use of plasma deposition at AP and concurrently feeding an organic precursor and a silver salt such as silver nitrate. This method was implemented using HMDSO and silver nitrate; the resultant coatings were effective in killing *E. coli*.[120,121] Other workers extended this to incorporating into SiO_x plasma polymers (from hexamethyldisiloxane, HMDSO) silver, zinc, and copper nanoparticles using their respective nitrates.[122] In another example, Ag nanoparticles were directly fed into the discharge zone to produce tetramethyldisiloxane-based plasma coatings with embedded silver nanoparticles and a relatively high loading ratio.[123] In a more recent study, direct atmospheric plasma deposition was used to form core-shell nanocapsules on a solid surface with silver as the core and polymer as the shell.[124] The coatings had two-phase kinetics of silver ion release consisting of a short-term burst release followed by a long-term slow release. The authors related release rates to the antibacterial efficiency of the coatings with their low cytotoxicity. A great deal of activity and the large number of papers published in recent years, in the use of AP plasma systems is not a surprise since the technology is much easier to apply to roll-to-roll manufacturing compared with low pressure-based processes.

2.4.2 | Multistep approaches

Limitations of the direct methods relate to control over coating structure and properties, which could be overcome using approaches that involve two or more steps. The pioneering report in this area involved the deposition of an amine-rich plasma polymer film using precursors such as allylamine and heptylamine.[125] The film can then be loaded with silver ions by soaking in a solution of silver nitrate. The silver ions are then reduced to silver nanoparticles by immersion of samples in an aqueous sodium borohydride solution. The resultant coatings loaded with silver nanoparticles proved to be very effective in killing medically relevant Gram-negative and Gram-positive pathogenic bacteria.[125,126] A major concept presented in this study, and then widely followed by researchers in the field, was to deposit a further plasma polymer layer, which served as a barrier overlayer to adjust release rates, on top of the silver nanoparticles loaded nanocomposite film. The thickness of the overlayer could be effectively used to control the kinetics of the release of silver ions, thereby eliminating toxicity issues in mammalian cells.[125] This approach was then used by other groups involving overlayers produces from a range of different precursors such as maleic anhydride,[127] polytetrafluoroethylene (PTFE) sputtering[128] or a mixture of ethylene (C_2H_4) and carbon dioxide (CO_2).[129]

Another two-step approach involves the combination of a plasma polymer film having appropriate functionalities and techniques such as electrostatic or covalent surface assembly.[130,131] For example, amine functional plasma polymer films acquire a positive charge at $pH < 8$. In an early study, silver nanoparticles synthesized in solution and passivated by polyvinyl sulphonate (PVS) were electrostatically adsorbed onto plasma polymer-coated solid surfaces. This was possible owing to the attractive interfacial electrostatic double-layer force between the positive charge of the amine plasma polymer and the negative charge of the PVS-capped nanoparticles.[131] This strategy was successfully utilized for surface immobilization of a range of negatively charged silver nanoparticles capped with 2-mercaptosucinic acid,[132] negatively charged phospholipids,[133] or hybrid nanoparticles.[134] The same approach can be extended beyond silver nanoparticles.[130,135] As part of the multistep approaches, the possibility to deposit multilayered structures should also be mentioned, which can allow greater amounts of silver to be loaded into coatings in a controllable manner. Such multilayers have been produced by the combination of plasma polymerization and magnetron sputtering.[136] Similar outcomes could also be achieved by combining plasma polymerization with

electrostatic self-assembly or covalent binding of nanoparticles from the solution.

There is no doubt that plasma polymer films containing silver nanoparticles are effective tools in eliminating bacterial surface colonization. However, from a clinical perspective, an important consideration is the effect of such antibacterial coatings on mammalian cells and tissues. Work demonstrated modulation of inflammatory responses, which can be positive or negative depending on the clinical context.[132–134] Studies involving stem cells demonstrated that plasma polymer coatings containing silver nanoparticles enhanced the adipogenic capacity of human bone-marrow-derived mesenchymal stem cells,[137] while mouse kidney-derived stem cell differentiation was directed towards podocyte lineages.[138] These studies indicate the need for research beyond the simple cytotoxicity assays conducted in most published work. The capacity of silver-containing plasma polymer coatings for regulating physiological processes also provides opportunities that could be explored by developing novel pathways to precisely control the rate of release and local concentration of silver ions and nanoparticles.

2.5 | Aerosol assisted AP PE-CVD processes

LP plasma processes to produce polymeric coatings of diverse compositions have been developed since the early 1960s for a wide range of potential and realized applications. The nonequilibrium conditions coupled with the low pressure (tens to hundreds millitorr) and other variables (monomer, power input, power modulation, etc.) allow the deposition processes to start and proceed with the substrate (and the coating) under controllable positive ion bombardment. This generally confers good adhesion on most substrates, as well as the tuneable composition and structure of the coatings. LP plasma processes are, however, limited by the requirement of sufficient volatility of the "monomer." While heating the monomer reservoir and the gas lines can increase to some extent the vapor pressure of the monomer and its flow rate into the discharge, this approach is not feasible for, for example, thermolabile or easily polymerizable monomers (e.g., acrylic acid), and does not achieve sufficient flow rates in large volume reactors.

Accordingly, much attention has been paid to AP plasma processes in recent years. AP plasma deposition processes have been developed for biomedical and other applications.[139] An interesting extension is the provision of the monomer or multiple components in the form of aerosol instead of the traditional vapor flow where the process vapor is fed into the discharge in the form of nanometric aerosol droplets formed with a buffer inert gas, generally He. Aerosol Assisted AP (AA-AP) PE-CVD processes, developed in the Flemish Institute for Technological Research (VITO)[140] in 2006, allow feeding AP deposition plasma processes with thermolabile high molecular weight monomers that could not be used in LP plasma deposition reactors. With this approach, indeed, aerosols of suspensions of nanoparticles (such as metal clusters) and of solutions of biomolecules (e.g., drugs, antibiotics, enzymes, etc.) can be fed into AP plasma reactors, leading to unique nano-composite and bio/nano-composite coatings, respectively, for potential applications as drug-release systems in general, and for antibacterial coatings in particular. The latest developments of the AA-AP-PE-CVD technique have been reviewed recently.[141]

3 | SUMMARY AND CONCLUSIONS

The processing advantages of plasma polymerization and the unique properties of plasma-deposited coatings continue to inspire a substantial body of research aiming to understand both the fundamental properties of such coatings and their potential applications. The need for control of interfacial interactions between biomaterials and biological environments is a key driver in efforts to utilize plasma polymers as thin coatings on biomedical devices, tissue engineering scaffolds, and implants. The interest in plasma polymers comprises both their intrinsic surface properties and chemistry and the use of specific chemical groups on the surface of plasma polymers to enable the covalent grafting of bioactive molecules. A prominent example is the need for antimicrobial coatings; to this end, plasma polymers per se and plasma polymers with surface-grafted antimicrobial molecules have been investigated. Another line of investigation comprises the use of plasma polymers as thin coatings carrying embedded bioactive molecules, nanoparticles, or metal ions that are released at controllable rates. Furthermore, additional plasma overlayers of controllable thickness have allowed tailoring of release rates of embedded bioactive molecules or metal ions.

In terms of plasma processing methodologies, there has been a pronounced increase in interest in processes at AP, on the basis of the processing advantage of avoiding the need for vacuum systems. The addition of the use of aerosols for feeding components into the plasma has further enhanced the utility of AP plasma processing for biomaterials coatings.

ACKNOWLEDGMENT

Open access publishing facilitated by The University of Adelaide, as part of the Wiley - The University of Adelaide agreement via the Council of Australian University Librarians.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: B. R. Coad, P. Favia, K. Vasilev, H. J. Griesser, *Plasma Processes Polym.* **2022**;19:e2200121.
https://doi.org/10.1002/ppap.202200121