# Bioactive Coatings

Subjects: Surfaces, Coatings & Films

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## Definition

In this entry, we compiled a variety of creative approaches to generate antimicrobial bioactive coatings. The benefits are very desirable: to create surfaces that either repel the attachment of viable microorganisms or kill microorganisms on contact without inducing inflammation or cytotoxicity to host tissues.

These coatings may consist of nanoparticles of pure elements (e.g. silver, copper, and zinc), sanitizing agents and disinfectants (e.g., quaternary ammonium ions and chlorhexidine), antibiotics (e.g., cefalotin, vancomycin, and gentamacin), or antimicrobial peptides (AMP).

Many bioactive coatings may involve unique delivery systems to direct their antimicrobial capacity against pathogens, but not commensals. Coatings may also contain multiple antimicrobial substances to widen antimicrobial activity across multiple microbial species.

**Table of Contents [Hide]**

## 1. Elements in Bioactive Coatings

Pure elements and metal salts have been used as effective antimicrobial agents against pathogenic microorganisms, including oral microorganisms and periodontal pathogens [1][2]. Antibacterial properties and their effectiveness to prevent bacterial attachment may differ significantly among different elements, depending on the target bacterial species [3]. Titanium and tin generally do not exhibit much antibacterial activity, whereas cobalt, nickel, copper, zinc, zirconium, and molybdenum do and, therefore, show promise as potential surface coatings of titanium implants .

Silver appears to be the most promising element, with strong antimicrobial activity while exhibiting minimal cytotoxicity to human oral cells [1]. For example, nanoparticles or composite nanoparticles of silver coated on titanium or incorporated into polyacrylate-based hydrogel or lactose-modified chitosan coatings on titanium inhibited Gram-positive and Gram-negative bacteria with little cytotoxicity to osteoblast-like cells and primary human fibroblasts [4][5][6][7][8]. Silver was also effective when incorporated into resins and dental materials. Silver nanoparticles (10–200 ppm) in denture liner material and silver nanoparticles (20.0–30.0%) in denture acrylic disks inhibited the growth of Candida albicans .[9][10]. Salts of silver have also exhibited antimicrobial capacity and 0.5% silver benzoate in resins and 0.5–25.0 µg/mL silver nitrate applied topically inhibited Streptococcus mutans, Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, Tannerella forsythia, Fusobacterium nucleatum ss vincentii, Campylobacter gracilis, Campylobacter rectus, Eikenella corrodens**,** and Aggregatibacter actinomycetemcomitans [2][11]. Differing methods have been used to prepare these nanoparticles. For example, Shankar et al. used Neem (Azadirachta indica) leaf broth to enhance the synthesis of gold nanoparticles, silver nanoparticles, and bimetallic gold/silver nanoparticles [12]. Ultrastructurally, a core–shell structure was formed; silver nanoparticles were on gold nanoparticles. They thought that this synthesis method could achieve rates of synthesis equal to that of conventional chemical methods.

Different studies have shown that other elements display antimicrobial activity with minimal cytotoxicity. Copper oxide nanocomposites in polyurethane inhibited methicillin-resistant Staphylococcus aureus (MRSA) [13]; hydrogenated copper films inhibited S. aureus and Escherichia coli, but not the adhesion and proliferation of MG-3 osteoblasts and NIH-3Te fibroblasts [14]; and zinc oxide in coatings

inhibited S. aureus and E. coli, but were compatible with the adhesion, proliferation, and differentiation of rat bone marrow stem cells[15]. Bismuthinetriyltris(oxy) tris(oxoazane) trioxide ($BiN_3O_9$) and bismuth (3+) triacetate ($C_6H_9BiO_6$) on titanium disks inhibited A. actinomycetemcomitans and MRSA but were not cytotoxic for MG63 osteoblast-like cells[16]. Selenium carbonated hydroxyapatite coatings prevented the establishment of P. aeruginosa and S. aureus biofilms, were not cytotoxic to MC3T3-E1 preosteoblasts, and enhanced cell proliferation [17]. Cobalt, copper, zinc, zirconium, molybdenum, and lead in resin resulted in a fourfold reduction of S. aureus and E. coli within 24 h compared to controls [3].

Diogo et al. assessed antimicrobial activity and cytotoxicity of a chlorophyll-based photosensitizer Zn(II)chlorine methyl ester ((Zn(II)$e_6$Me) [18]. The chlorophyll derivative Zn(II)$e_6$Me was antimicrobial for mixed biofilms and had minimal cytotoxicity for human apical papilla cells.

## 2. Antiseptics and Disinfectants in Bioactive Coatings

Antiseptics and disinfectants are effective antimicrobial agents [19] when incorporated in polymers and implant coating materials. They rapidly kill microorganisms via disruption of phospholipid bilayers; removal of divalent cations; release of LPS; disruption of cross-linked proteins in the cell membrane; inactivation of membrane-bound enzymes; and damage to cross-linked intracellular proteins, RNA, and DNA [19].

Compounds containing chlorhexidine, a strong disinfectant that prevents initial bacterial adhesion, have been applied in calcium phosphate phases to titanium alloy (e.g., Ti6Al4V) surfaces [20]. These surfaces were formed by a co-deposition process of both phases where chlorhexidine interacted with the deposition and transformation of calcium phosphate phases in the coating. For high chlorhexidine contents, coatings consisted of chlorhexidine crystals coated by nanocrystalline hydroxyapatite [20].

Disinfectants of the guanidine and polyhexanide families are also very effective against a variety of Gram-positive and Gram-negative bacteria and have potential as effective antimicrobial agents against oral microorganisms [21]. Guanidine incorporated into homo- and copolymers of 2-aminoethylmethacrylate in solution or in coatings were not cytotoxic to cells and inhibited E. coli and Bacillus subtilis [21]. Half maximal inhibitory concentration (IC50) was 9 µg/mL and minimal inhibitory concentrations (MIC) were 16 µg/mL. Polyhexanide encapsulated in hyaluronic acid inhibited hyaluronidase producing stains of S. aureus (MIC, 62.5 µg/mL) and E. coli (MIC, 250.0 µg/mL) [22].

Although not cytotoxic for human gingival fibroblasts, compounds containing quaternary ammonium, phosphonium, or pyridinium ions, like poly-(4-vinyl-N-hexylpyridinium bromide) appear to be weaker disinfectants and implant coatings have only moderate antimicrobial activity for oral microorganisms like Streptococcus mutans or Streptococcus sanguinis [23].

## 3. Antibiotics in Bioactive Coatings

Antibiotics can also be used in bioactive coatings to prevent peri-implant diseases. Antibiotics may act by altering microbial cell wall, nucleic acid, or protein synthesis, resulting in cell envelope damage and loss of structural integrity; double stranded DNA breaks; inactivation of DNA-dependent RNA synthesis; disrupted cellular energetics; and/or production of harmful hydroxyl radicals involving alterations in central metabolism [24]. Antibiotics that act on microbial membranes and/or inhibit cell wall or protein synthesis have been used as effective constituents in bioactive coatings to prevent peri-implant diseases. Generally, two strategies have been adopted. One strategy involved the continued slow release of antibiotics from coatings containing free antibiotics. Vancomycin incorporated into chitosan and deposited onto titanium to be released in a biologically active form inhibited the growth of S. aureus [25]; vancomycin incorporated into polymer multilayer films inhibited the growth of S. aureus [26]; and cefalotin incorporated into apatite and deposited onto titanium inhibited S. mutans[27].

Another strategy involved the immobilization of antibiotics to implant surfaces. This strategy worked well to repel the attachment of viable microorganisms or kill microorganisms on contact with the implant

surface to prevent the onset of peri-implant mucositis. Protein synthesis inhibitors like tobramycin, gentamicin, and tetracycline have been used for this purpose. Tobramycin immobilized on microporous octacalcium phosphate on titanium inhibited P. aeruginosa over 4 h [28]. Gentamicin incorporated into poly d,l-lactide polymeric coatings inhibited the growth of S. aureus [29], while 20.0% tetracycline incorporated into chitosan coatings and bonded to titanium (737.0 + 125.7 μg/cm$^2$) inhibited S. epidermidis and A. actinomycetemcomitans, but was not cytotoxic to osteoblastic cells or fibroblasts [30].

Nystatin and Amphotericin B are antibiotics that act on fungal membranes. They bind to ergosterol and form concentration-dependent transmembrane pores. Potassium, sodium, hydrogen, and chloride ions leak from the cytoplasm leading to eventual fungal cell death. Both 1.0% nystatin and 0.1% Amphotericin B in polymers applied to denture materials inhibited C. albicans biofilms [31].

Rai et al. synthesized spherical gold nanoparticle (52–22 nm) and cefaclor complexes [32]. This complex had potent antimicrobial activity against both S. aureus and E. coli with MICs of 10 mg/mL and 100 mg/mL, respectively. The combined action of Au and cefaclor were thought to interfere with the synthesis of peptidoglycan and creating pores in the microbial cell walls.

## 4. AMPs in Bioactive Coatings

AMPs are relatively small peptides that contain cationic, anionic, or amphipathic amino acid residues. These peptides attach to microbial surfaces and may kill microorganisms by a variety of mechanisms: formation of lethal pores; disruption of membrane integrity; or cytoplasmic penetration to inhibit cell wall synthesis, alteration of septum formation in the cytoplasmic membrane, binding to DNA, inhibition of enzymatic activity, DNA, RNA, and/or protein synthesis [33]. AMPs are widely distributed throughout species of the Monera (e.g., Eubacteria), Protista (e.g., protozoans and algae), Fungi (yeasts), Plantae (plants), and Animalia (e.g., insects, fish, amphibians, reptiles, birds, and mammals) kingdoms [34]. They include groups of synthetic peptide mimetics, hybrid peptides, peptide congeners, stabilized peptides, peptide conjugates, and immobilized peptides [35]. Natural, as well as synthetic AMPs derived from lactoferrin [28][36], LL-37 [37], and beta defensins [38], may be active against Candida species and other microorganisms, and have the potential to be applied in bioactive implant coatings.

AMPs can be adsorbed to surfaces, coated on surfaces, or covalently bonded to functionalized surfaces to prevent microbial biofilm formation. These alternatives open the door to different therapeutic strategies. One strategy is to incorporate AMPs into films for continuous release over time at relevant concentrations. Films that allow heavy drug loading and favorable release kinetics to prevent attachment of microorganisms are desirable [26]. Another strategy is to use nondiffusible AMPs by means of covalent immobilization to material surfaces. It has been shown that AMPs tethered to functionalized poly-(ethylene glycol) can form a nonadhesive peptide layer that kills bacteria on contact [37]. AMPs immobilized to titanium surfaces have been tested to shorten the period of osseointegration and to reduce colonization of periodontopathogens to implant surfaces [39][40][41]. Immobilized histatin alone or conjugated peptides of histatin 5/titanium binding peptide and lactoferricin/titanium binding peptide reduced colonization of P. gingivalis and enhanced mRNA expression of runt-related transcription factor 2 (Runx), Osteopontin (OPN), and alkaline phosphatase (ALPL) in osteoblastic cells. Runx2 is an inducer of osteoblast and chondrocyte differentiation [42], OPN is important in cell communication and matrix mineralization [43], and ALPL is involved cementum mineralization [44]. AMP Tet213 loaded on a thin microporous coating of calcium phosphate on titanium had antimicrobial activity against Gram-positive and Gram-negative bacteria with $10^6$-fold reductions in CFU within 30 s [45]. It has been also demonstrated that calcium phosphate–Tet213 is a more efficient antimicrobial coating than calcium phosphate–MX226, calcium phosphate–hLF1-11, or calcium phosphate–tobramycin.

Following incubation of calcium phosphate-coated implants with equimolar concentrations of Tet213, the commercially developed antimicrobial peptide MX-226, hLF1-11, or tobramycin inhibited bacterial growth. Also, Chrysophsin-1 and -3 incorporated into acrylic coating systems exhibited antimicrobial

activity against both Gram-positive and Gram-negative bacteria in vitro, which may be applicable for future dental applications to reduce bacterial colonization and a subsequently favorable tissue response [46].

The mechanisms of activity of AMPs bound to surfaces or incorporated into materials remain unknown [33]. The chemical coupling procedure, length of spacers, peptide orientation, and peptide concentration are all important contributing factors [47]. The antimicrobial activity distinctly decreased with reduction of the spacer length. Still, peptides are thought to insert into the target membrane by using an exchange of membrane-stabilizing bivalent cations, which contributed to the antimicrobial effect [48]. Other studies suggest that the surface actions of AMPs were sufficient for their lethal activities [49].

## 5. Antimicrobial Substances with Future Potential in Bioactive Coatings

There are other antimicrobial substances that have potential as additives in bioactive coatings to prevent peri-implant diseases due to their proven activity against oral microorganisms. Phenylalkyne compounds, arylamide compounds, and the mimetic mPE have potent antifungal activity against planktonic cultures and biofilms of Candida species [50] and antimicrobial activity against biofilms of A. actinomycetemcomitans and P. gingivalis [51]. It has also been shown that S. mutans competence stimulating peptide (CSP) attached to an antimicrobial peptide domain can kill S. mutans [52]. We found that coupling an antibody specific to the outer surface of P. gingivalis strain 381 to sheep myeloid antimicrobial peptide (SMAP28) selectively killed P. gingivalis in an artificially generated microbial community containing P. gingivalis, A. actinomycetemcomitans, and P. micros [53]. In other studies, AMPs have also been tethered to resins or brush layers with proposed uses as contact-active cationic antimicrobial surfaces [48][49].

Furthermore, AMPs and lysozyme have been encapsulated within silica or titanium nanoparticles to create bio-nano-composite materials with antimicrobial activity for use as broad-spectrum antifouling materials or in cosmetics with sunscreen properties [54]. Another AMP suitable for incorporation into coatings for dental implants is human lactoferrin 1-11 (hLF1-11), which is derived from the first 11 amino acids of human lactoferrin.

Some antimicrobials have shown promise in combination with bone regeneration enhancers. Surfaces with co-immobilized arginylglycylaspartic acid (RGD) and PHSRN peptides were found to significantly improve osteoblast responses [55]. Surfaces containing gentamicin and bone morphogenetic protein-2 showed enhanced antibacterial activity and osseointegration compared to a control [56].

Some lipids are also active against oral microorganisms and have potential as additives to bioactive coatings or creams to prevent peri-implant and other oral diseases. Long chain bases (sphingosine, dihydrosphingosine, and phytosphingosine) and short chain fatty acids (sapienic acid and lauric acid) have exhibited antimicrobial activity against a variety of Gram-positive bacteria, Gram-negative bacteria, and oral bacteria, by inducing ultrastructural damage and altered microbial metabolism [57][58][59]. Recent work suggests these lipids are also likely involved in innate immune defense against epidermal and mucosal bacterial infections [60][61]. However, little is known yet about the spectrum of lipid activity against oral bacteria and Candida species or their mechanisms of action.

## 6. Future Directions

Development and testing of prosthetic surface coating strategies represents a relevant and emerging topic in contemporary research with great potential for therapeutic application in dentistry and other clinical disciplines. Although promising results have been reported, the vast majority of the evidence available to date emanates from in vitro studies and each approach has advantages and disadvantages.

For endodontic applications, a promising methodology is the use of photodynamic therapy (PDT) as an alternative to classical endodontic irrigation solutions and antibiotics for the treatment of apical

periodontitis [62][63]. Diogo et al. first assessed the ability of PDT to improve root canal disinfection[62]. They concluded that the antimicrobial activities of PDT were most effective when used with toluidine blue and methylene blue at 660 nm wavelength with a 400 nm diameter of intracanal fiber. Diogo et al. then assessed the antimicrobial approaches to improve PDT efficiency [63]. Two favorable approaches emerged for endodontic purposes that included drug delivery systems using nanoparticles and photosensitizer solubilizers.

For oral implantology applications, antimicrobial prosthetic surfaces should not only prevent bacterial adhesion, but allow or even enhance the attachment, proliferation, and differentiation of host cells to promote adequate peri-implant healing and long-term health [64]. Future investigations in this field should focus on clinical translation with the purpose of assessing the performance and biosafety of different antimicrobial coatings aimed at reducing microbial growth and biofilm formation on implant prosthetic surfaces.

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